Diatomite as a potential drug carrier for Itraconazole and improvement in release control

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Abstract:

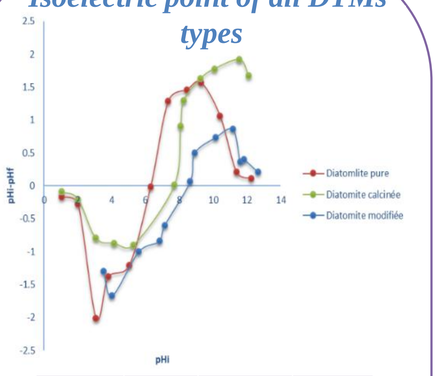
Many obstacles associated with the use of conventional drug delivery systems have led to the development of new various micro/nano sized drug carriers. These carriers are designed with the aim to improve therapeutic outcomes and/or reduce drug's adverse effects, by providing protection of the entrapped drug against in vivo degradation, releasing drug in desired man-ner, improving drug solubility and/or reducing its immunogenicity. Additionally, their small sizes make these carriers when loaded with the bioactive molecules suitable and allowing their vectorization to the target site. In this work, Diatomite (DTM) was used as a support material for Itraconazole (ITZ) which is known for its fairly low side effects. The major drawback in the therapeutic application and efficacy of ITZ as oral dosage forms is its very low aqueous solubility. Three Binary systems were prepared using different proportions of the two components and where tested for the ability of DTM to improve the solubility of ITZ in aqueous and in organic media. The efficacy of encapsulation was demonstrated by UV analysis. The prepared systems were characterized using UV-Vis, FTIR, MEB, AFM and Optical microscopy. Moreover, the study of kinetics and mechanism of drug release in the gastric medium exhibit a sustained profile during 02 hours.

Introduction

Today smart technologies are used in several domains. Most of them are related with pharmaceutical industry and biomedical applications. The most recent are poorly soluble drug in aqueous solvents, that's why the modern medicine address a formidable challenge to resolve this hurdle by developing a new drug delivery systems. The main objective is to enhance the solubility, the drug efficiency and minimized the side effects. Itraconazole is hydrophobic agent having low side effects and widely prescribed for normal and immunocompromised hosts with serious fungal infections.[1]

Therefore, in the last years, emerging natural porous materials for biomedical applications have also been suggested to overcome the shortcomings of the synthetic porous materials like Diatomite. This magic bullet are characterized by excellent biocompatibility, non-toxicity and thermal stability[2]. The aim of this research was to enhance the solubility capacity of itraconazole using pure Diatomite silica and the modified one with several techniques(calcination and chemical methods) as encapsulation system. The efficacy of encapsulation was demonstrated by standard methods such as extraction and UV analysis. The prepared systems were characterized using UV-Vis, FTIR, MEB, AFM and Optical microscopy. Moreover, the study of kinetics and mechanism of drug release in the gastric medium exhibit a sustained profile during a time of two hours.

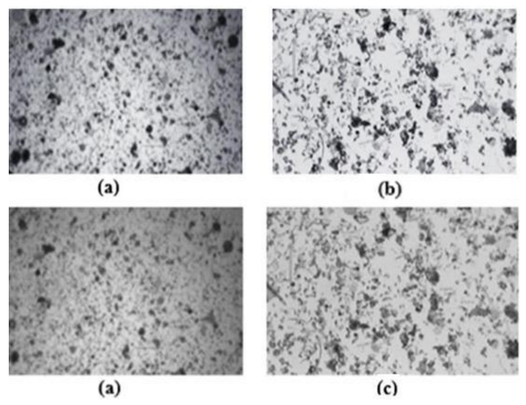
Isoelectric point of all DTMs types



DTM types	Pure	Mod by $AL_2(SO_4)_3$	Cal
IZ. P	6.3	8.6	7.7

Table 3 : DTM isoelectric point (pure, modified, calcined)

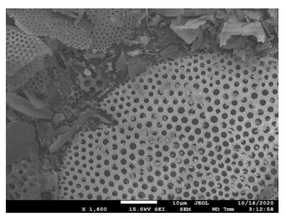
Optical microscopy analysis



By comparing the pur DTM (a) with the chemically modified DTM (b) and calcined (c)

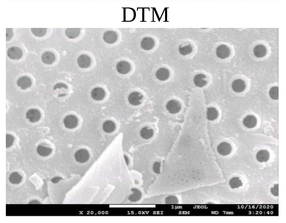
The appearance of the identical particle

Scanning electron microscope analysis

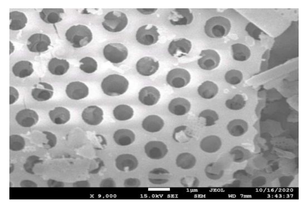


DTM

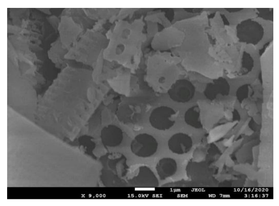
- It can be seen that DTM mod and DTM cal encapsulate ITZ present a higher porosity than DTM pur.
- This confirms that pur DTM has a low absorbing capacity due to the reduced diameter of the pores.



ITZ/DTM pur CH_2Cl_2



ITZ/DTM mod CH_2Cl_2



ITZ/DTM cal CH_2Cl_2

AFM images

➢DTM

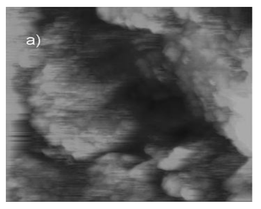


Fig 16: AFM image (5x5 µm) of DTM: a) topography [1]

➢ ITZ/DTM mod CH_2Cl_2

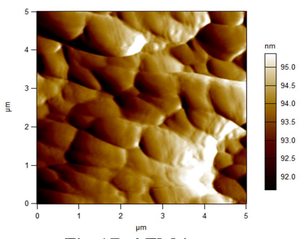


Fig 17: AFM image (5x5 µm) of ITZ/DTM mod CH_2Cl_2 a) topography.

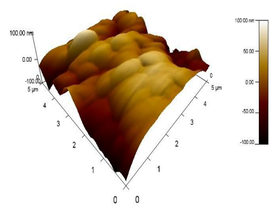


Fig 18: AFM 3D surface topography (500x500nm) of ITZ/DTM mod CH_2Cl_2

➢It can be seen from the fig 16 where the AFM micrographs of the diatomite are presented that small diatomite particles are compacted into the pellet. A sponge like structure with small pore sizes that can be noticed from topography picture [1]

➢We can notice a surface with a higher rugosity in AFM picture of Diatomite /ITZ system fig 17. RMS = 28.053 nm

Results and discussion

UV-vis analysis

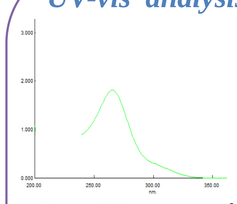


Fig 1: UV spectrum of ITZ/DMT pure (CH_2Cl_2)

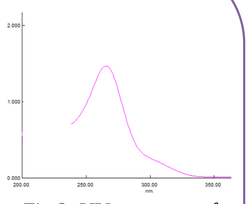


Fig 2: UV spectrum of ITZ/DMT mod (CH_2Cl_2)

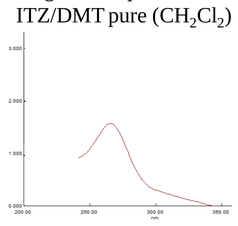


Fig 3: UV spectrum of ITZ/DMT cal (CH_2Cl_2)

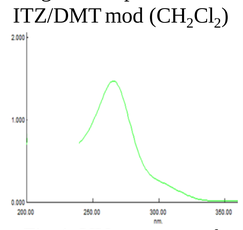


Fig 4: UV spectrum of ITZ/DMT cal (CH_3OH/HCl)

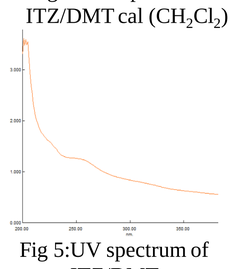


Fig 5:UV spectrum of ITZ/DMT mod(CH_3OH/HCl)

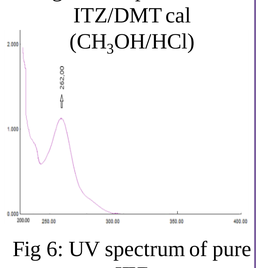
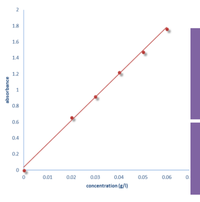


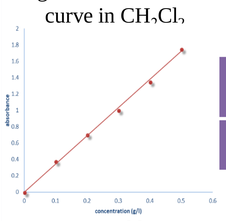
Fig 6: UV spectrum of pure ITZ



DTM	Pure	Mod by $AL_2(SO_4)_3$	Cal
% included	0,2%	100%	100%

Fig 7: ITZ calibration curve in CH_2Cl_2

Table 1: %included of ITZ/DTM in CH_2Cl_2



DTM	Mod by $AL_2(SO_4)_3$	Cal
% included	93,16%	83,44%

Fig 8: ITZ calibration curve in CH_3OH/HCl

Table 2: %included of ITZ/DTM in CH_3OH/HCl

Release results of SPORANOX 50mg tablets:

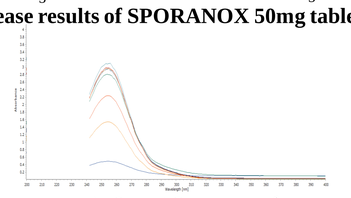


Fig 9: UV Spectrum of SPORANOX® 50mg tablet during

FTIR analysis

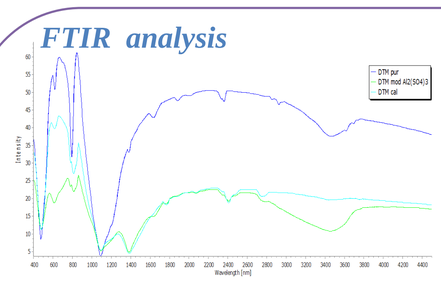


Fig 11:FTIR spectrum of DTMs (pure, calcined and modified)

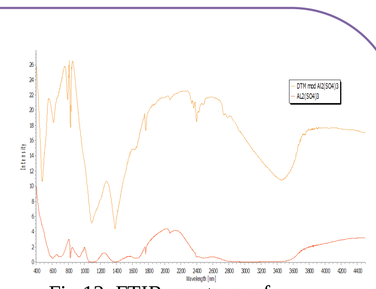


Fig 12: FTIR spectrum of :
-DTM mod by $AL2(SO_4)_3$
-$AL2(SO_4)_3$

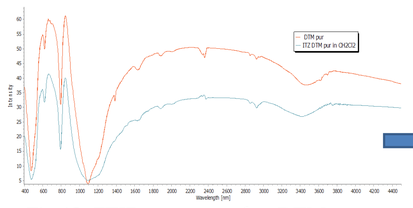


Fig 13: FTIR spectrum of : - DTM pur
- ITZ/DTM pur CH_2Cl_2

The absence of the characteristic peaks of ITZ was noted. This confirms that pure DTM has a low absorbing capacité due to the reduced diameter of the pores (very low % encapsulation of ITZ just 2%).

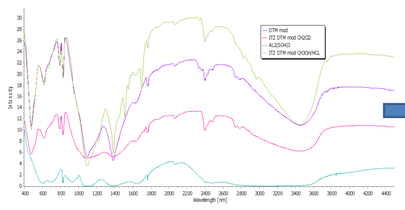


Fig 14: FTIR spectrum of :
-DTM mod - Al2(SO4)3
-ITZ/DTM mod CH2Cl2 -ITZ/DTM mod

The appearance of the characteristic bands of ITZ at 1510, 1700, 3068 cm^{-1} in the FTIR spectrum ITZ/DTM mod CH3OH/HCl and also in ITZ/DTM mod CH_2Cl_2 at 1609 and 1697 cm^{-1}(Fig 14).

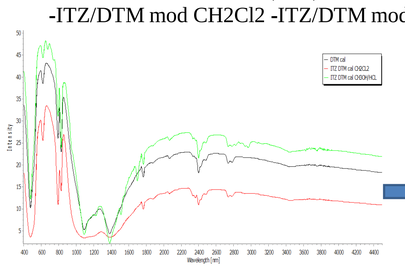


Fig 15: FTIR spectrum of : -DTM cal
-ITZ/DTM cal CH_2Cl_2
-ITZ/DTM cal CH_3OH/HCl

The FTIR spectra of ITZ / DTM calcinated CH_3OH / HCl show a peaks at 1510, 1700 and 3130 cm^{-1} and broad band between 1000 cm^{-1} and 1200 cm^{-1} of ITZ / DTM calcinated CH_2Cl_2 these observations validate and justify the result of the calcinated DTM encapsulation.

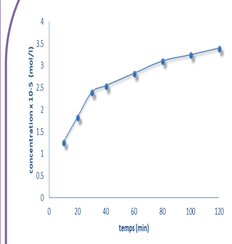
Conclusion

This study demonstrates the feasibility of naturally and modified DTM microparticles to be used as drug carrier for drug delivery of ITZ. Versatile and successful modifications of DTM surface by calcination and chemical modifications were successfully demonstrated. The loading capacity and in vitro drug release properties of DTM microparticles were successfully obtained by enhancing the solubility of ITZ and by sustaining its release[3].

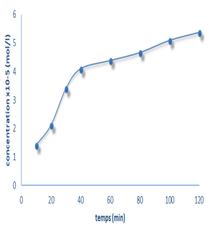
Release kinetics in the gastric meduim

Physical mixture ITZ/DTM

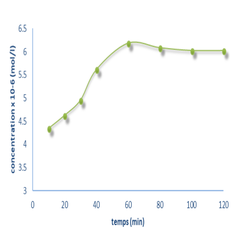
ITZ/DTM mod complex



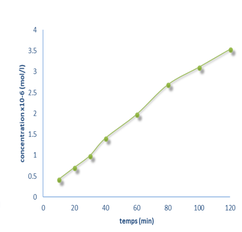
Releae profile ITZ/DTM mod



Releae profile ITZ/DTM cal

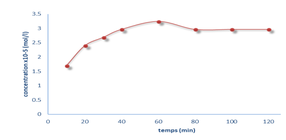


Releae profile ITZ/DTM mod (CH_2Cl_2)



Releae profile ITZ/DTM mod (CH_3OH/HCl)

ITZ/DTM cal complex



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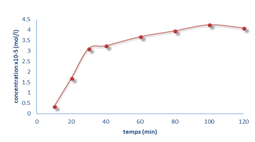
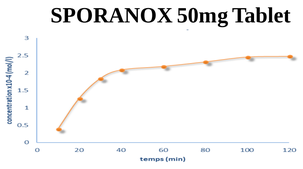


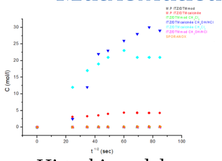
Releae profile ITZ/DTM cal (CH_3OH/HCl)

SPORANOX 50mg Tablet

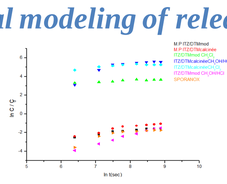


SPORANOX Releae profile

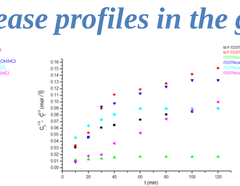
Mathematical modeling of release profiles in the gastric meduim



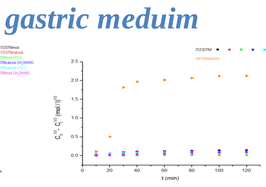
Higuchi model



Korsmeyer-Peppas model



Hixson-Crowel model



Hixson-Crowel model for ITZ/DTM and SPORANOX®

the optimal model for the liberation kinetics

- the one that has an R^2 closer to1.
- DTM mod and the DTM cal liberate ITZ by a diffusion mechanism more than by erosion.

Reference

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[3]M. Bariana, M. S. Aw, M. Kurkuri, et D. Losic, « Tuning drug loading and release properties of diatom silica microparticles by surface modifications », *Int. J. Pharm.*, vol. 443, nº 1-2, p. 230-241, févr. 2013, doi: 10.1016/j.ijpharm.2012.12.012.

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