Supercritical fluid technology shows promising potentials for enhancement of dissolution for Class II drugs

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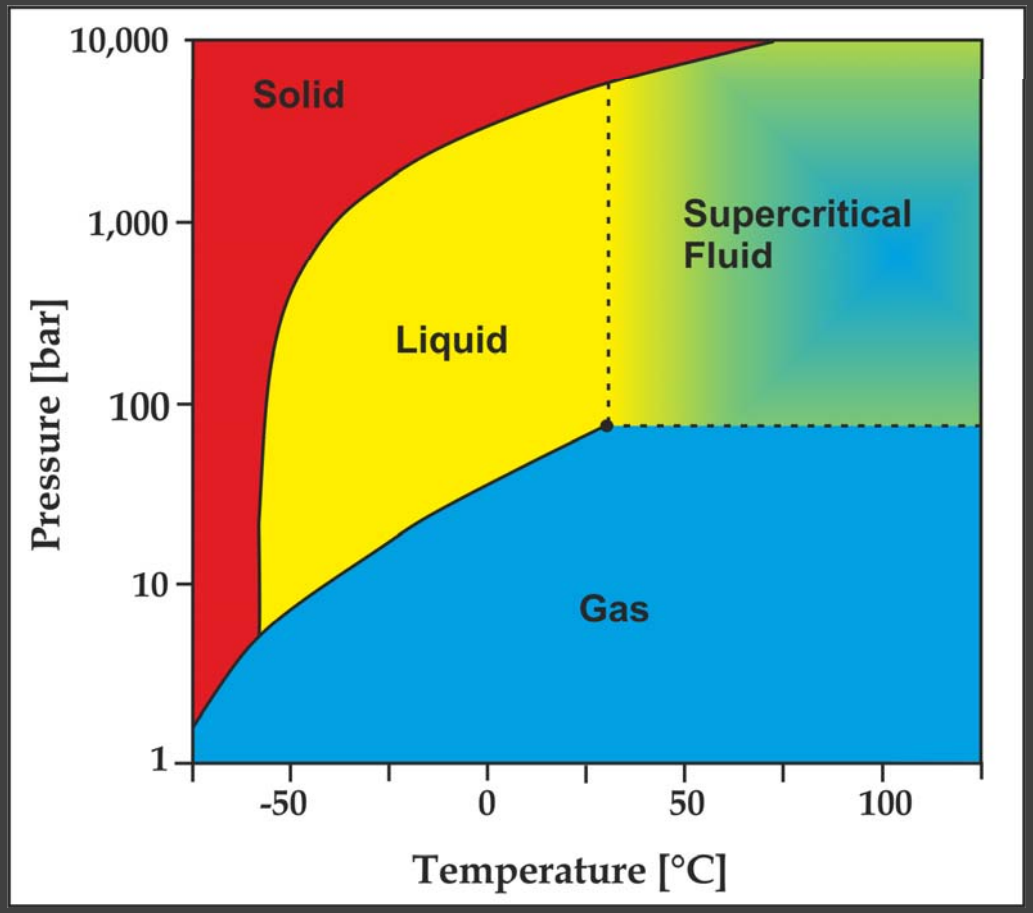
Supercritical Fluid Technology (SFT)



Supercritical Fluid Technology (SFT)

Applications Investigated in JUST Labs

- **Solid Dispersions.**
- **Complexation with Cyclodextrins.**
- **Aerogel Production.**
- **Polymeric Modifications.**
- **Taste Masking.**
- **Extraction.**

Using SFT in Preparation of Solid Dispersions

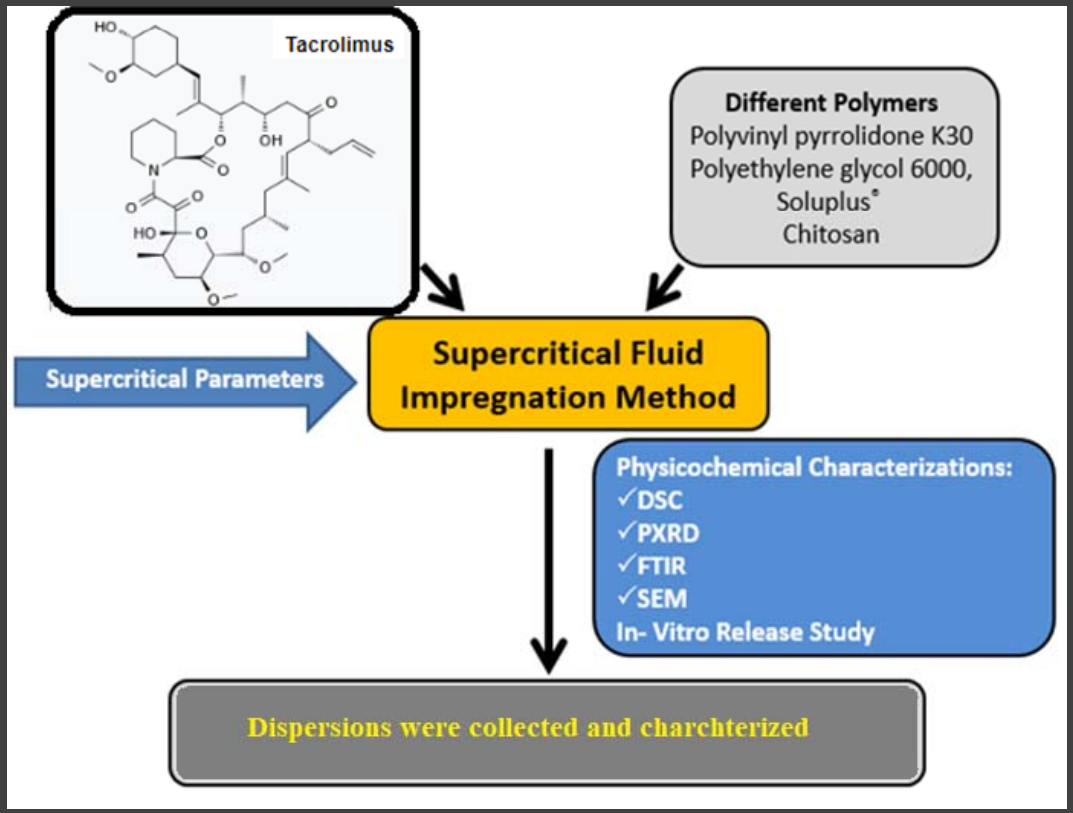
Why supercritical technology can replace many conventional techniques in preparation of solid dispersions?

- Stability of most drugs (thermolabile & photosensitive drugs).
- Rapid method.
- Low running cost.
- No residual solvents: can be used as a solvent-free method (Impregnation).
- Easy handling for some polymers.
- Swelling and plasticization phenomena of polymers in the supercritical state.

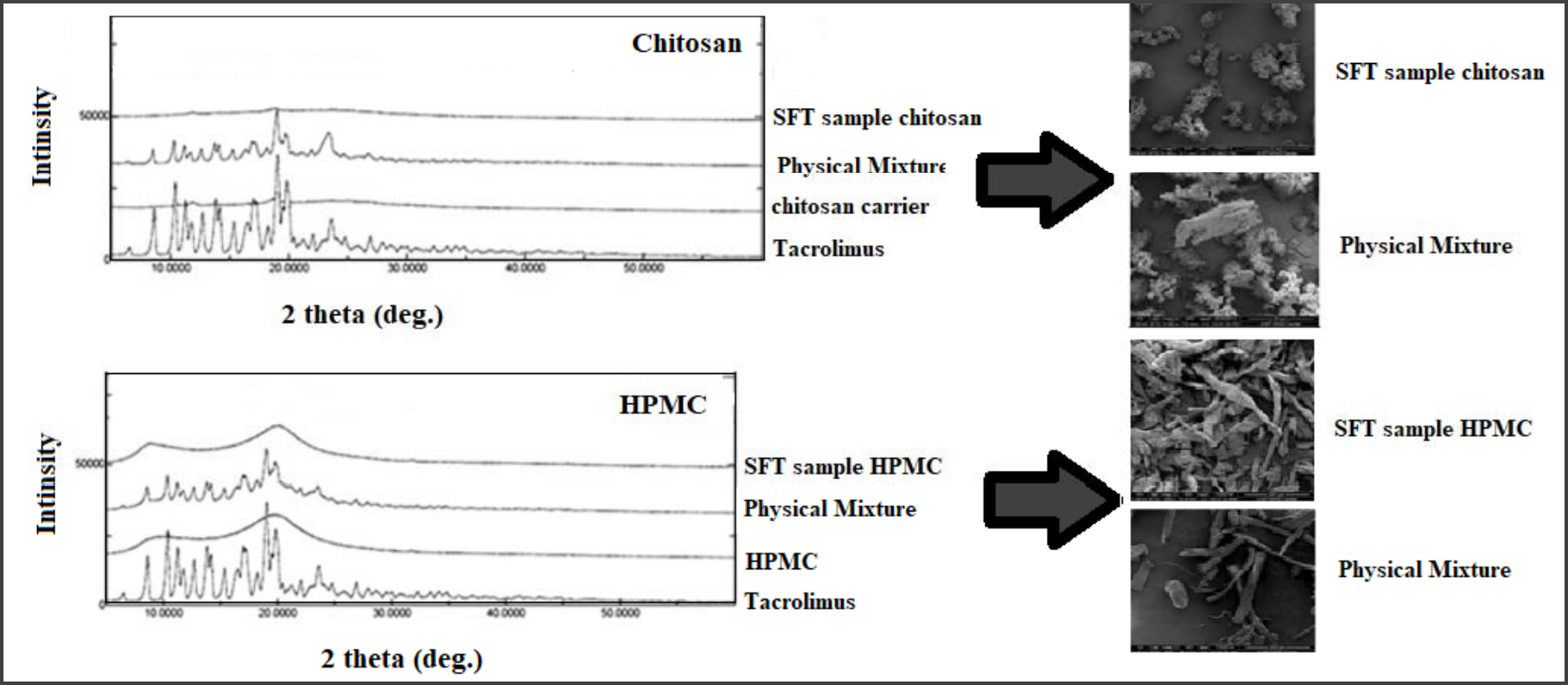
Using Supercritical Fluid Technology (SFT) in Preparation of Tacrolimus Solid Dispersions

- **Tacrolimus is an immunosuppressant agent that suffers from poor and variable bioavailability. This can be related to limited solubility and dissolution. The main objective of this study is to use SFT to prepare solid dispersions of tacrolimus in order to enhance its dissolution. SFT was selected since it offers several advantages over conventional techniques such as efficiency and stability.**

Methodology



Results


Chitosan
Intinsity
50000
0
10.0000
20.0000
30.0000
40.0000
50.0000
2 theta (deg.)
SFT sample chitosan
Physical Mixture
chitosan carrier
Tacrolimus
HPMC
Intinsity
50000
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30.0000
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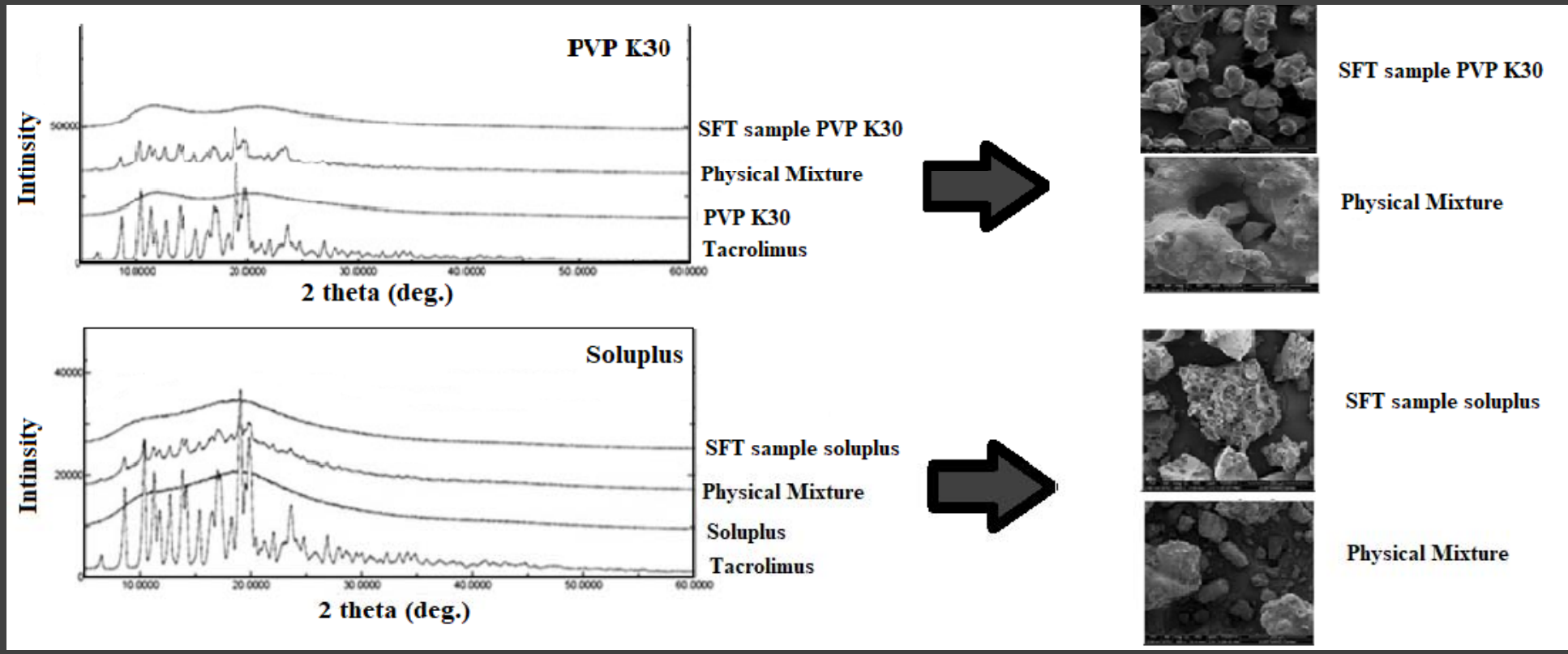
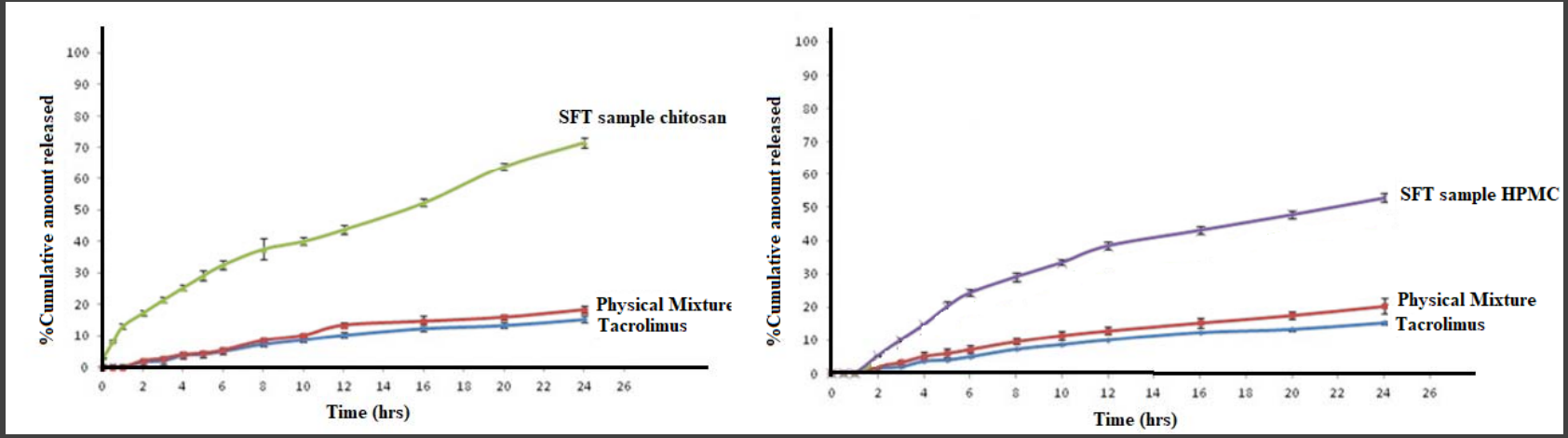
2 theta (deg.)
SFT sample HPMC
Physical Mixture
HPMC
Tacrolimus
SFT sample chitosan
Physical Mixture
SFT sample HPMC
Physical Mixture

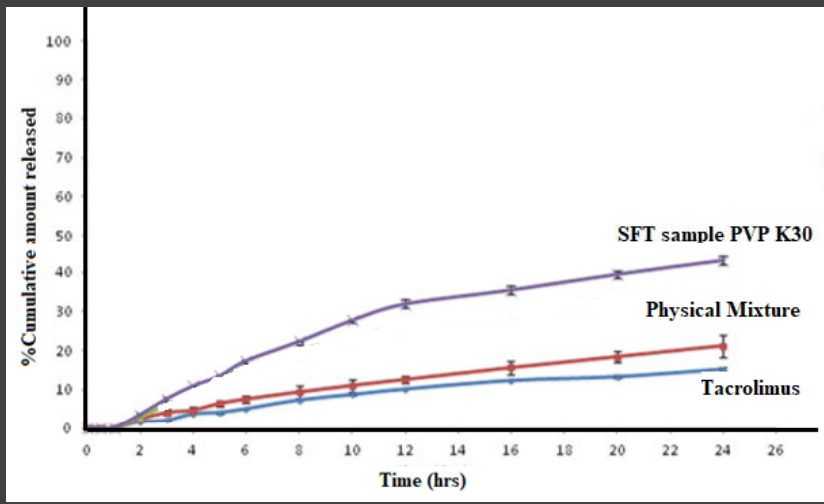
Results

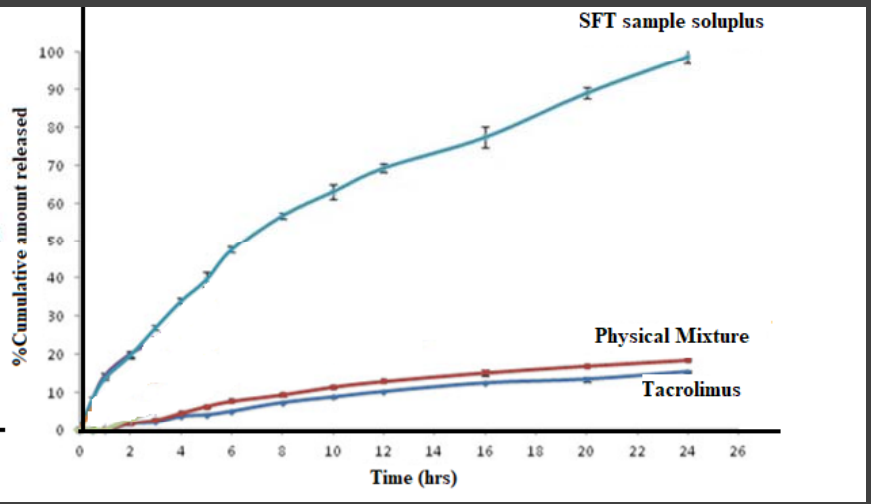

PVP K30
Intinsity
SFT sample PVP K30
Physical Mixture
PVP K30
Tacrolimus
2 theta (deg.)
SFT sample PVP K30
Physical Mixture
Soluplus
Intinsity
SFT sample soluplus
Physical Mixture
Soluplus
Tacrolimus
2 theta (deg.)
SFT sample soluplus
Physical Mixture

Results


%Cumulative amount released
Time (hrs)
SFT sample chitosan
Physical Mixture
Tacrolimus

%Cumulative amount released
Time (hrs)
SFT sample HPMC
Physical Mixture
Tacrolimus


%Cumulative amount released
Time (hrs)
SFT sample PVP K30
Physical Mixture
Tacrolimus


%Cumulative amount released
Time (hrs)
SFT sample soluplus
Physical Mixture
Tacrolimus

Factors affecting loading efficiency:

- **Loading time.**
- **Temperature.**
- **Pressure.**

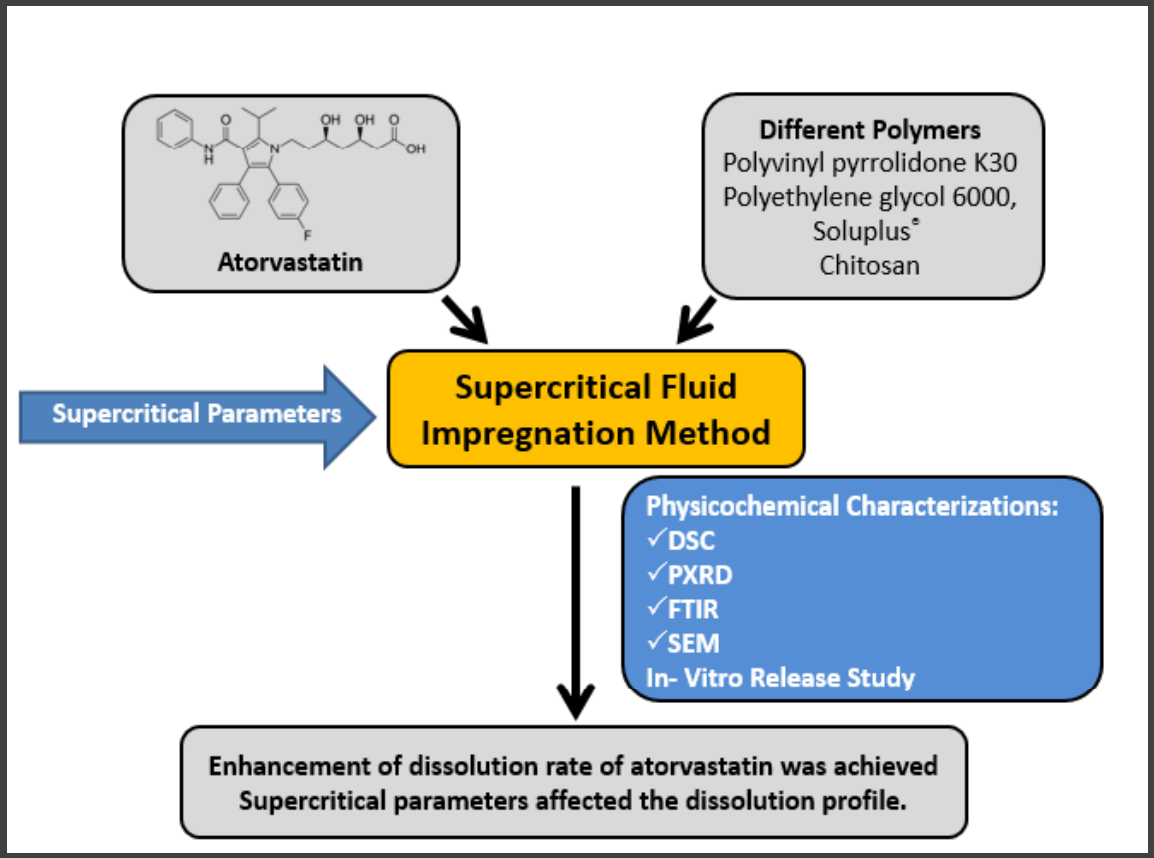
Results

- **Significant improvement for the release profile was achieved for the prepared dispersions.**
- **Better release achieved in the Soluplus® dispersions which reached maximum cumulative release equal to 98.76% after 24 h.**
- **Drug precipitated in its amorphous form in all prepared SFT dispersions.**
- **All dispersions were chemically and physically stable, yet stability studies proved to be affected by the type of polymer.**

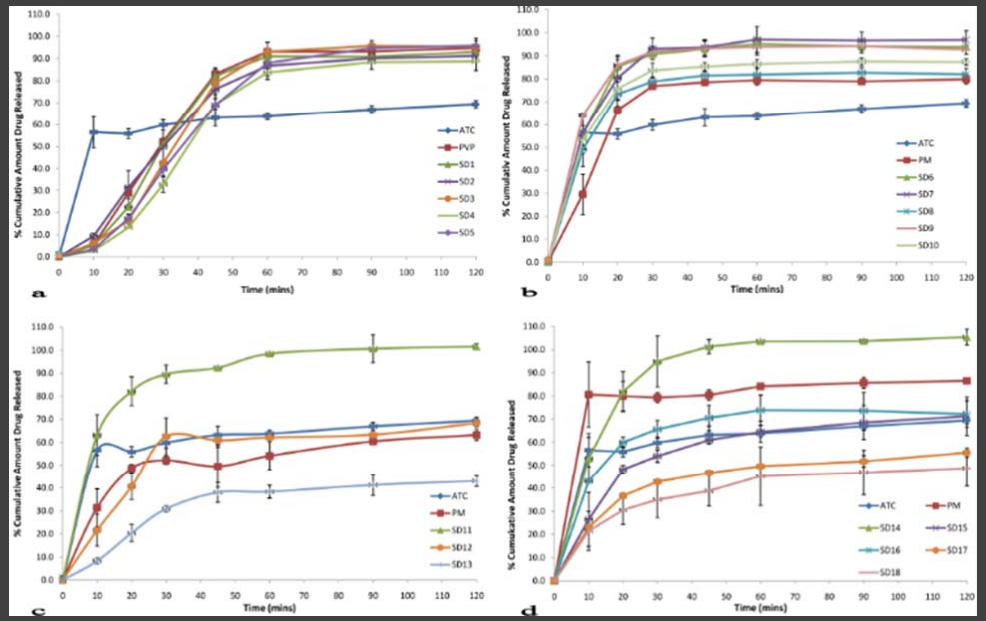
Conclusions for Tacrolimus study

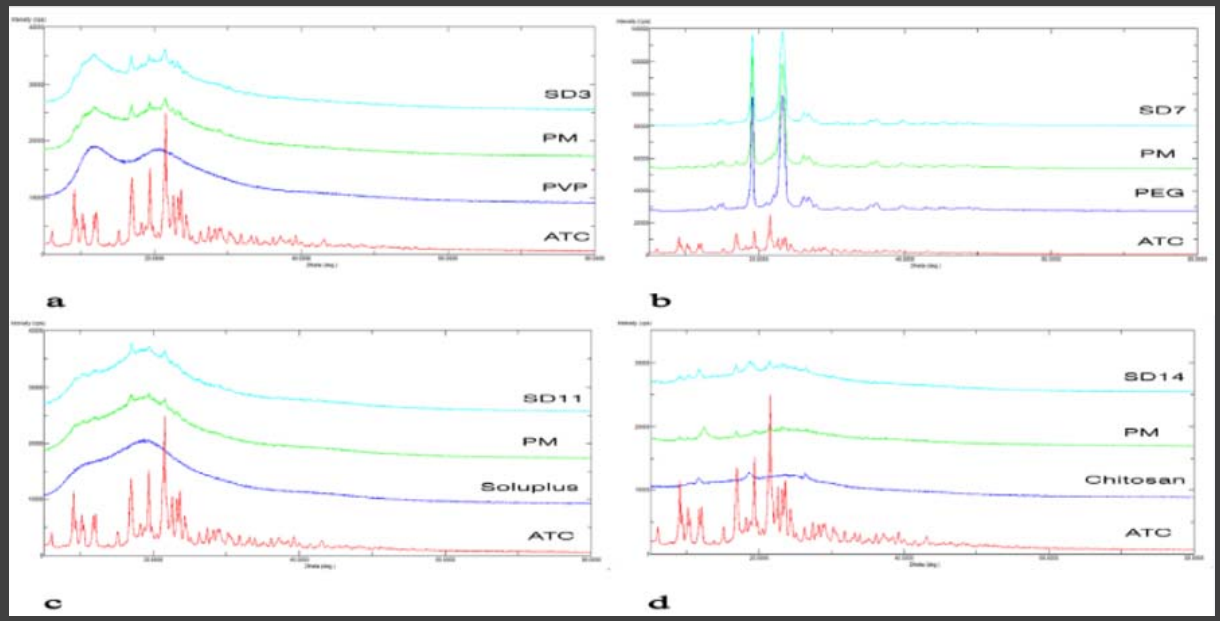
- **SFT was successfully used to prepare dispersions of tacrolimus that exhibited higher dissolution than raw drug.**
- **Dissolution rate and stability are affected by the type of the polymer.**

Employing Supercritical Fluid for Preparation of Dispersions for Atorvastatin



Atorvastatin





Results

- **The used polymers enhanced the dissolution rate of atorvastatin.**
- **Supercritical parameters affected the dissolution profile and drug loading efficiency of the prepared dispersions.**
- **HPLC method indicated the stability of the PEG, Soluplus® and chitosan-based dispersions.**
- **PVP was not stable and a sticky paste formed.**
- **PXRD showed similar patterns for PEG-based dispersions after exposure to storage condition, while the intensity of atorvastatin peaks increased after three months of storing for Soluplus® and chitosan dispersions.**

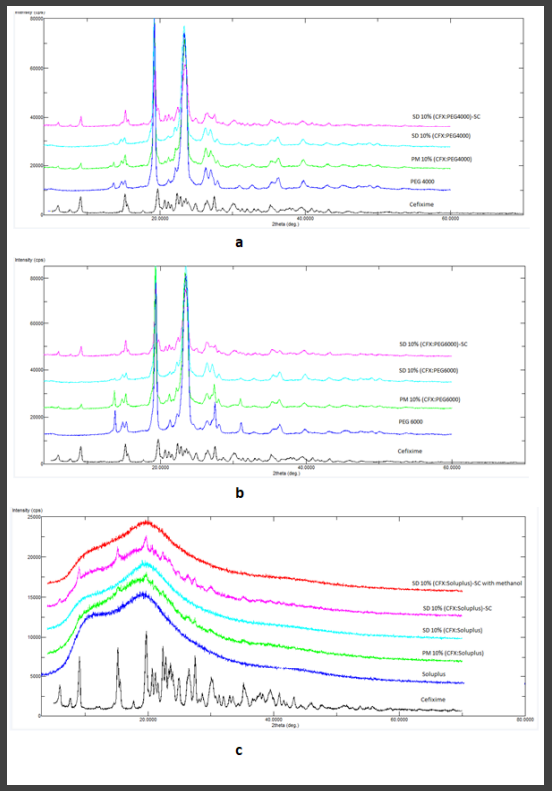
Results

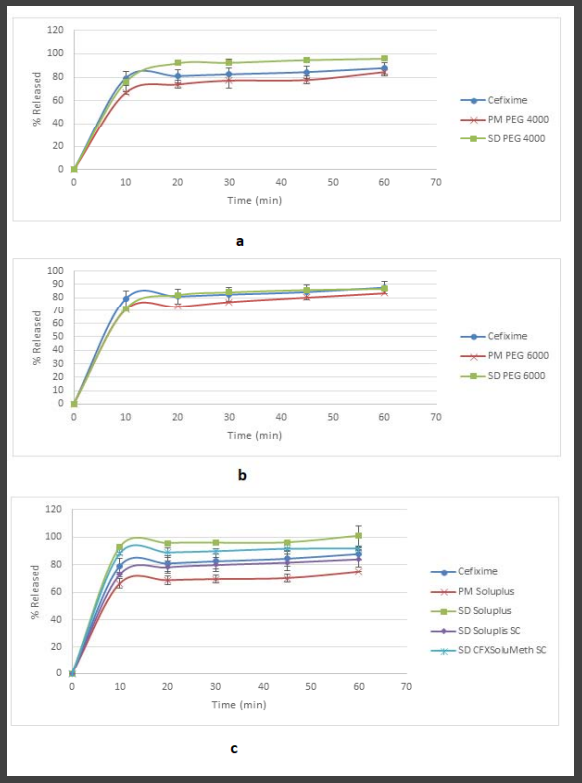
- **A good loading efficiency was obtained for all the polymers using SFT.**
- **Enhancement of dissolution rate of the drug was achieved compared to corresponding physical mixtures.**
- **The drug was present in its crystalline form inside the prepared dispersions.**
- **Best enhancement of dissolution profile was obtained using Soluplus®.**

Conclusions for Atorvastatin study

Although, SFT technology proved to have great potential to prepare dispersions for class II drugs, yet the physicochemical properties of the drug and polymer should be considered.

Employing Supercritical Fluid for Preparation of Dispersions for Cefixime trihydrate Dispersions



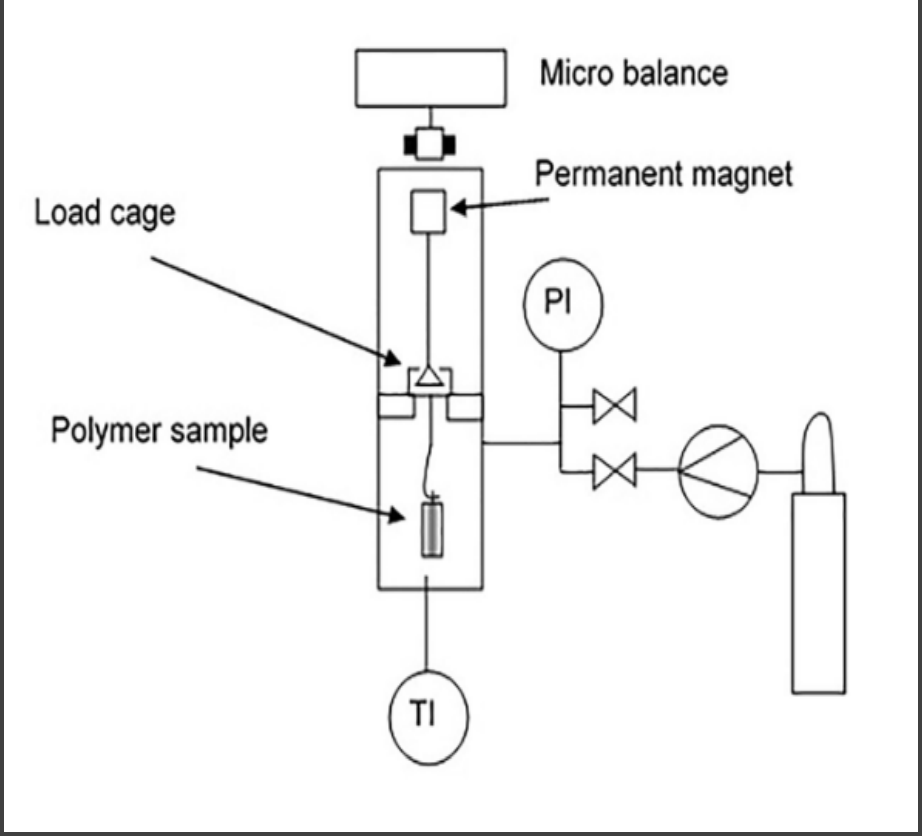


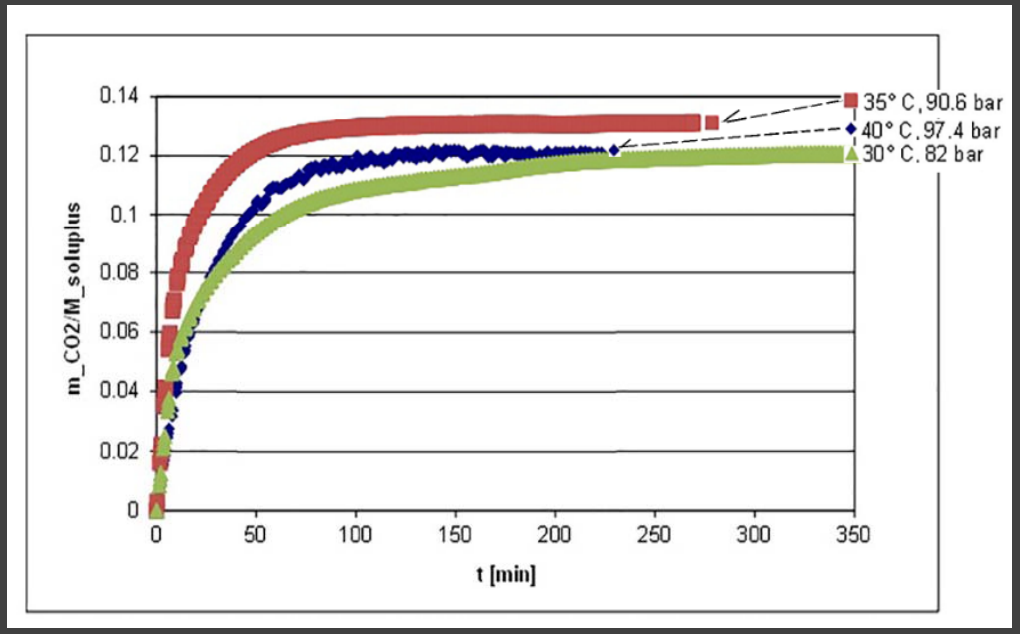
Conclusions

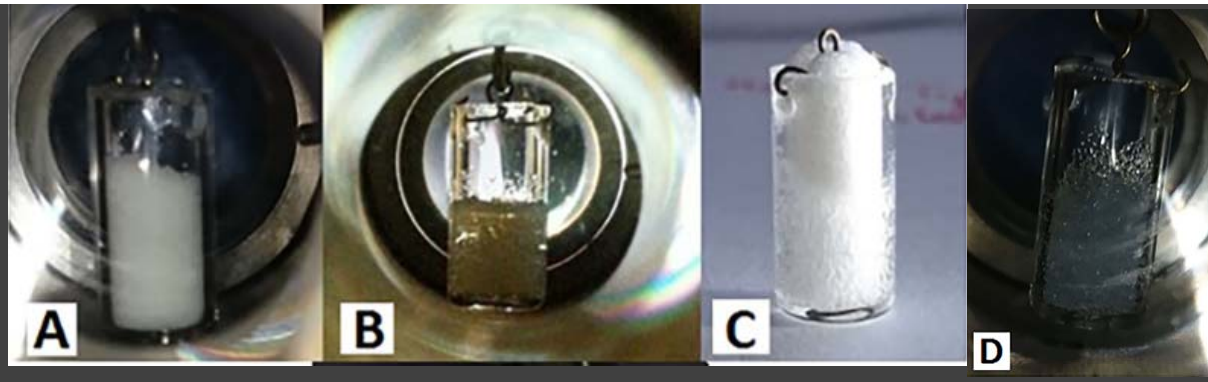
Although, SFT technology proved to have great potential to prepare dispersions for class II drugs, yet the physicochemical properties of the drug and polymer should be considered.

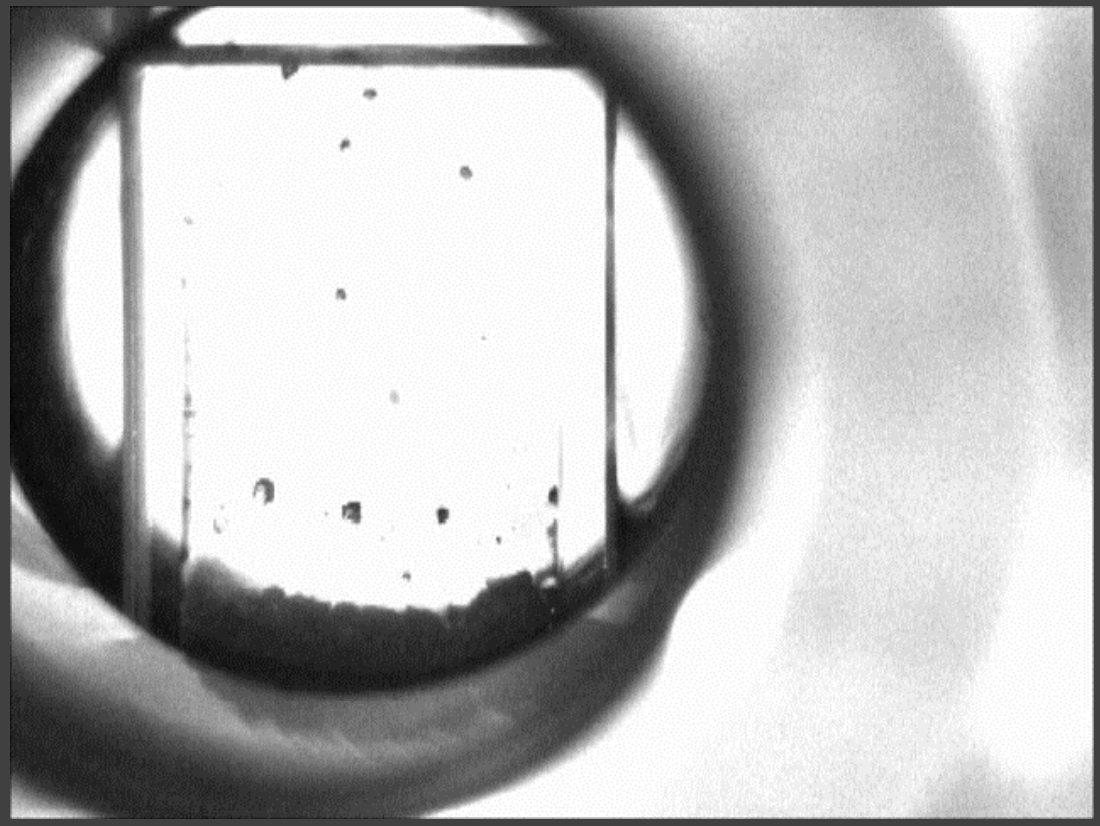
Addition of small amounts of Co-solvent (methanol) resulted in precipitation of amorphous form of cefixime trihydrate and enhancement of accumulative release percentage.

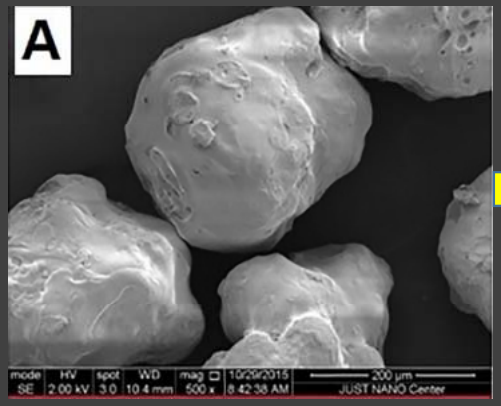
SFT Provides a Promising Technology For Preparation of Soluplus® Dispersions

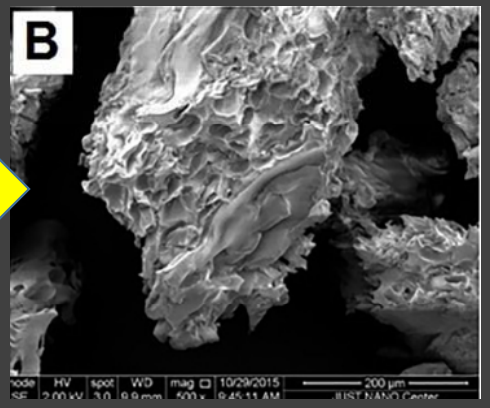



0.14
0.12
0.1
0.08
0.06
0.04
0.02
0
m_CO2/M_soluplus
0
50
100
150
200
250
300
350
t [min]
35° C, 90.6 bar
40° C, 97.4 bar
30° C, 82 bar

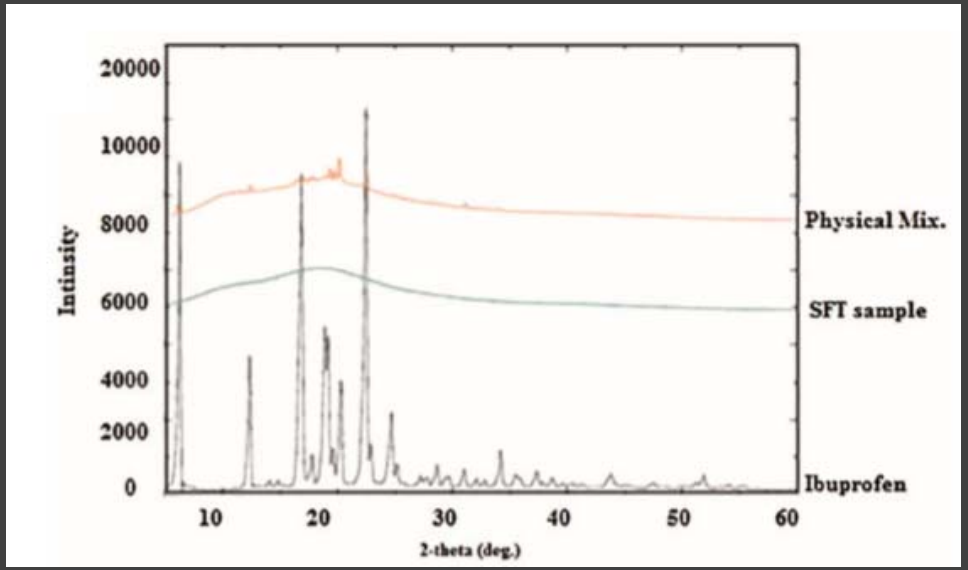

A
B
C
D

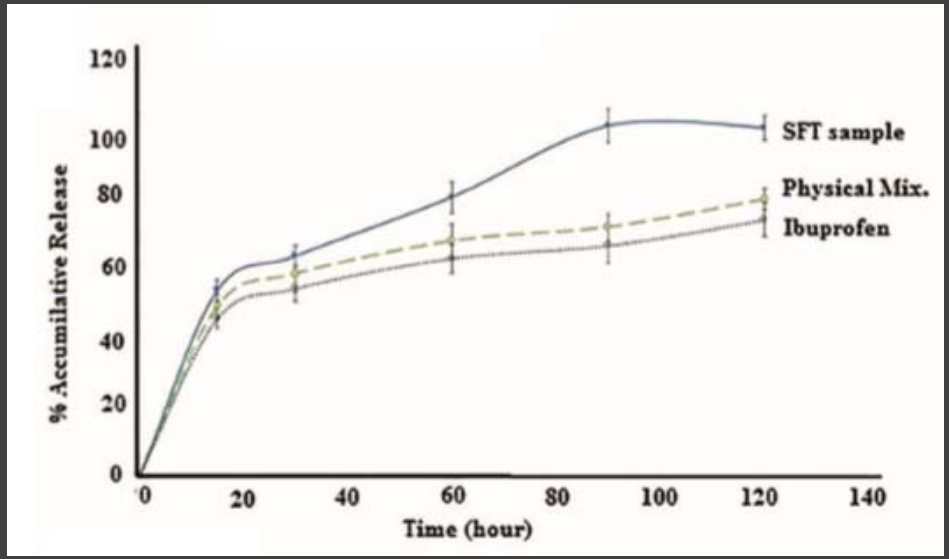



A


B

Ibuprofen Impregnation in Soluplus®

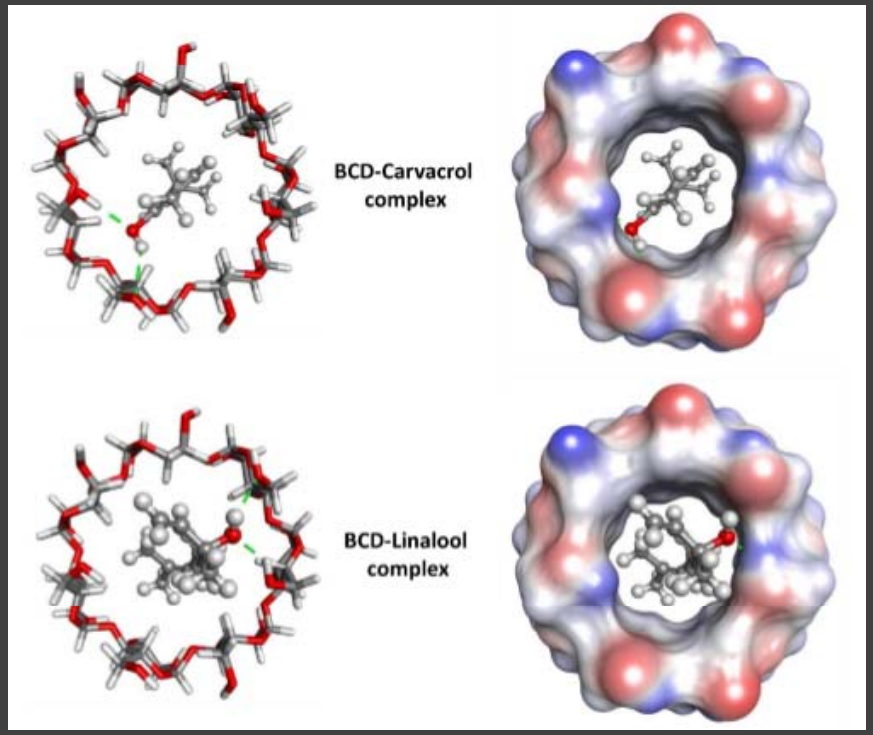




Conclusions for Soluplus® study

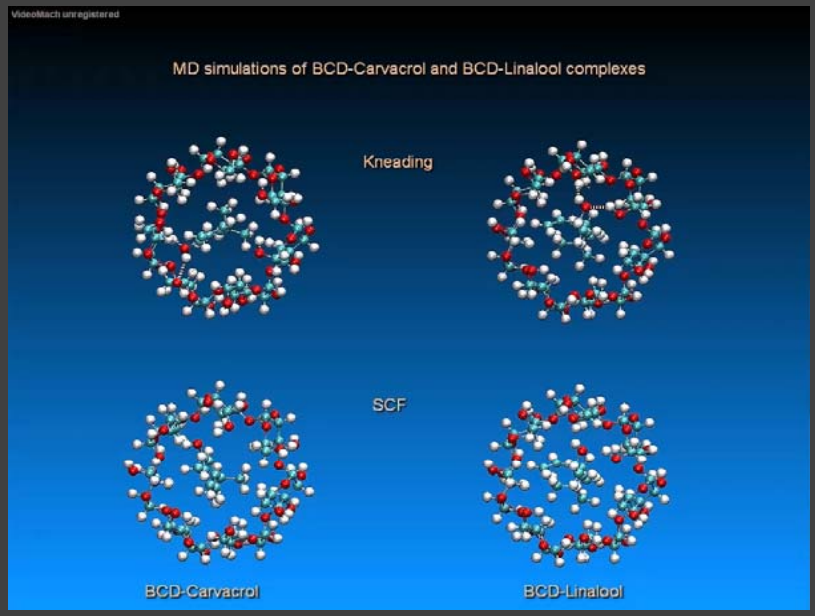
- Supercritical carbon dioxide is a promising technology in preparing amorphous solid solutions and dispersions of low-soluble drug at temperatures that do not exceed 45°C in less than 2h, which is of a great advantage to be used for thermolabile drugs as an alternative production method. The advantages of using this technology for Soluplus® formulations is the high sorption capability of carbon dioxide inside the polymer which will cause foaming of the polymer, expansion of the polymer intermolecular spaces and rapid diffusion of the dissolved/dispersed drug inside the polymer during supercritical conditions. Upon depressurization process, the drug will precipitate at the amorphous form accompanied by foaming of the polymer.

Using SFT in Preparation of Cyclodextrin Complexes



Experimental and Computational Comparative Study of The Supercritical Fluid Technology (SFT) and Kneading Method in Preparing β-Cyclodextrin Complexes With Two Essential Oils (Linalool and Carvacrol)

SFT offered many advantages as a potential complexation method compared to kneading technique. Its simplicity in applications which did not require any solvent is a significant benefit. Despite that, guest molecule entrapment was more efficient in conventional kneading method for both studied oils. All analysis performed in this study proved better complexation for the samples prepared using kneading method. Computational analysis had confirmed and explained the results obtained by experimental analysis. In conclusion, results here did not show any evidence of enhanced stability using the SCF technique compared to the conventional kneading method.

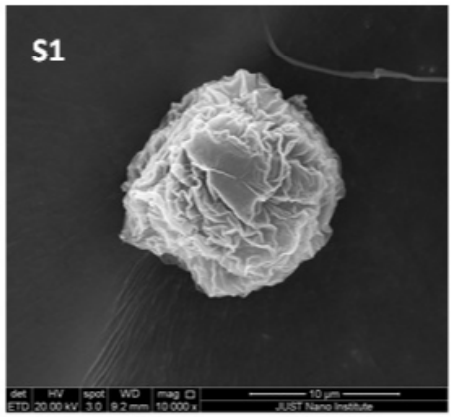


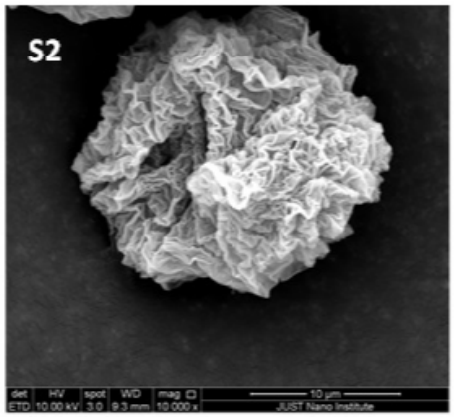
Aerogel Production
Nanoporous Carriers

- **The solvent is eliminated using supercritical fluid (SCF) technology to maintain the structure of the gel and to prevent the pore collapse phenomenon by protecting the dried product against cracking and shrinkage.**
- **Polysaccharide based aerogels combined the unique properties of aerogel and the attractive properties of polysaccharides which allows tailoring them to the targeted application. Due to their availability, surface properties, diverse functionality, low toxicity, biocompatibility and biodegradability they have been proposed for wide range of challenging applications. For instance, tissue engineering.**

Polysaccharide Based Aerogels

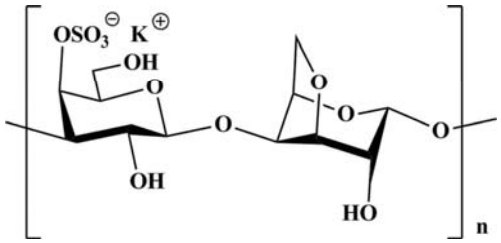
- Chitosan aerogels.
- Alginate aerogels.
- Carrageenan aerogels.
- Composite polymers.





Carrageenan

- Carrageenan , a family of high molecular weight polysaccharides polymers, composed of a linear chain of two alternating α-(1–3) and β-(1–4) linked D-galactosyl residues.



- Carrageenan extracted from various species of red seaweeds (red algae).

- The most important and commercially available Carrageenan types are kappa (κ), iota(ι), and lambda (λ).

- The difference between the three types is in the degree of sulphation, which will affect their properties.

Effect of processing parameters on preparation of carrageenan nanoporous (aerogel) microparticles

- In this work, the production of carrageenan based aerogel from different commercial available precursor as microparticles is reported.
- To the best of our knowledge, the preparation of carrageenan aerogel microparticles using emulsion gelation technique were firstly prepared in our lab.

Methodology

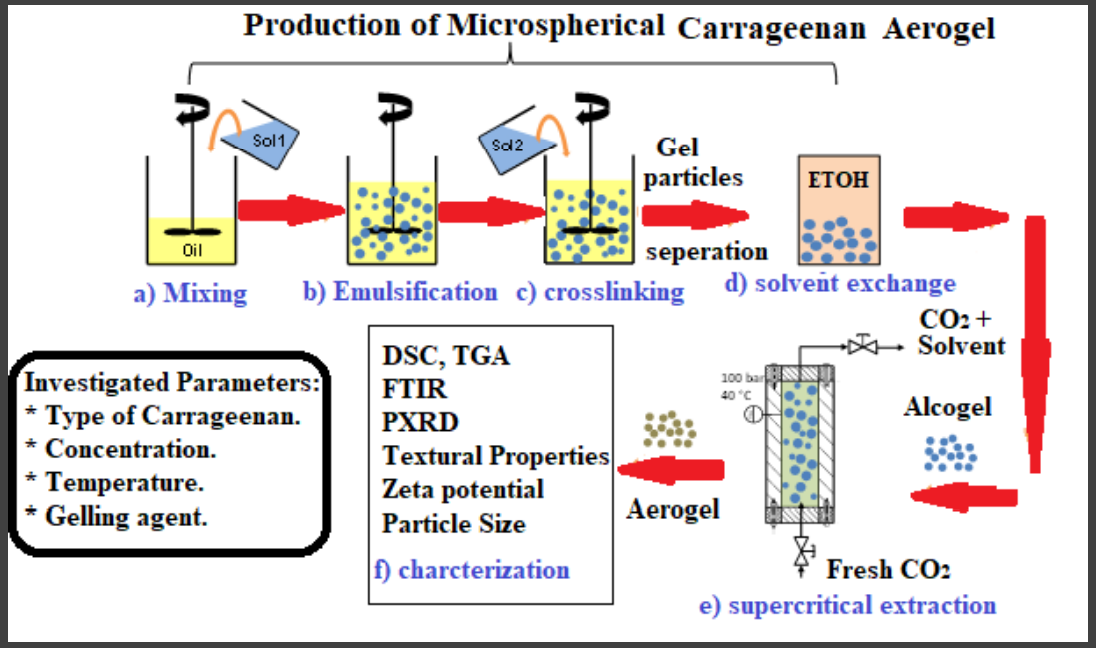
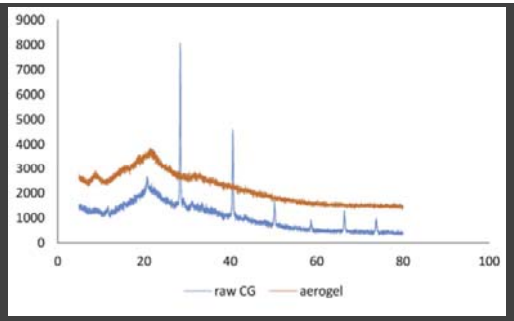


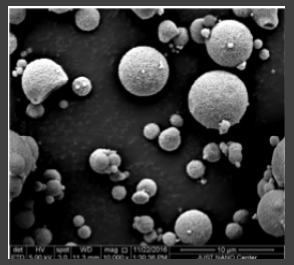
Table 1
Samples IDs and preparation conditions in this work.

Sample ID	type	Conc. wt%	cross-link wt%	Temp °C	Surfactant wt%
S1	suitable	4%	2.00% KCl	90	1% Span® 80
S2	suitable	3%	1.50% KCl	90	1% Span® 80
S3	suitable	2%	1.00% KCl	90	1% Span® 80
S4	suitable	4%	0.25% KCl	90	1% Span® 80
S5	suitable	4%	0.50% KCl	90	1% Span® 80
S6	suitable	4%	1.00% KCl	90	1% Span® 80
S7	suitable	4%	4.45% KI	90	1% Span® 80
S8	suitable	4%	1.85% K_2CO_3 (1.85%)	90	1% Span® 80
S11	suitable	2%	1.00% KCl	90	2% Span® 80
S12	suitable	4%	No cross linker	90	1% Span® 80
I1	type I	2%	1.00% KCl	65	2% Span® 80
I2	type I	2%	2.00% KCl	65	2% Span® 80
I3	type I	2%	3.00% KCl	65	2% Span® 80
I4	type I	2%	1.00% KCl	75	2% Span® 80
I5	type I	2%	1.00% KCl	90	2% Span® 80
I6	type I	2%	$CaCl_2$(eq to 1% KCl)	65	2% Span® 80
I7	type I	2%	$AlCl_3$(eq to 1% KCl)	65	1% Span® 80
I8	type I	4%	No cross linker	90	2% Span® 80
K1	kappa	2%	1.00% KCl	90	1% Span® 80
K2	kappa	4%	No cross linker	90	2% Span® 80

Results and Discussion

- **Effect of carrageenan type:** Affected surface charge and pore volume with no effect on particle size. BEST Kappa.
- **Biopolymer concentration:** Increasing the biopolymer concentration yield better aerogels in terms of textural properties.
- **Cross linker concentration:** It was noticed that the maximum surface charge was obtained when 1 wt.% of the cross linker was used. This have a direct effect on the aggregation of the particles, the larger the surface charge the less the aggregation tendency
- **Effect of preparation temperature:** Increase Temp. decreased particle size.

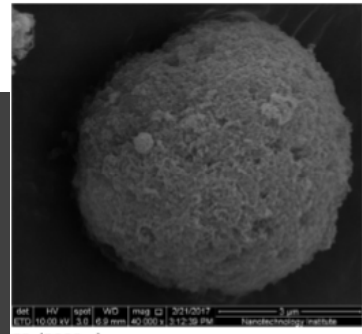




Effect of processing parameters on preparation of carrageenan nanoporous (aerogel) microparticles

- **In conclusion, biodegradable aerogel**

micro-spherical particles based on three different commercial available carrageenan were produced. Depending on the process parameters the surface area of the produced aerogel ranged between 33 and 174 m^2/g, the average pore volume and pore sized were 0.35 cm^3/g and 12.34 nm respectively. The produced Nano-porous material shows potential characteristic for drug delivery application.



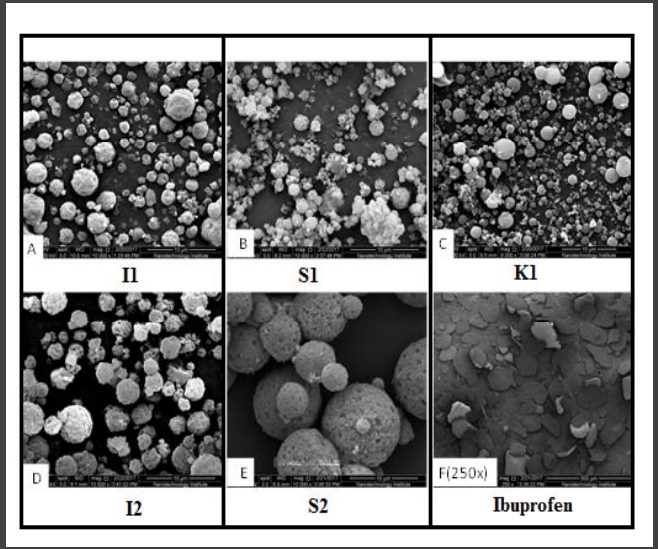
S8 (2000 x)

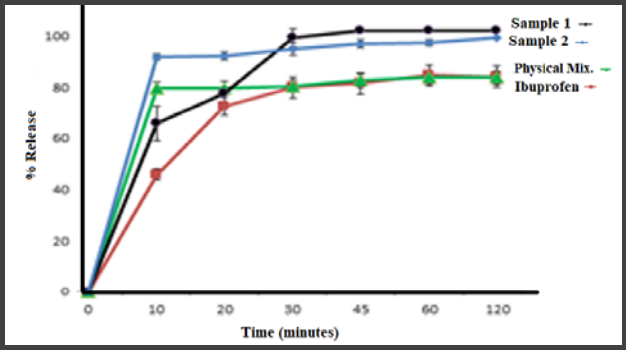
Investigation of Carrageenan Aerogels as a Potential Nanoporous Drug Carrier

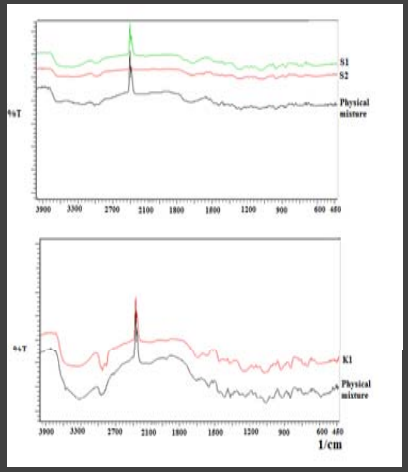
- **The study aimed to investigated potentials of carrageenan aerogels as potential drug Nanoporous carrier.**
- **Investigated drugs were Ibuprofen, Meloxicam, Celecoxib, and Atorvastatin were used as a model drugs.**
- **Ibuprofen has been selected as a model drug to be presented here.**

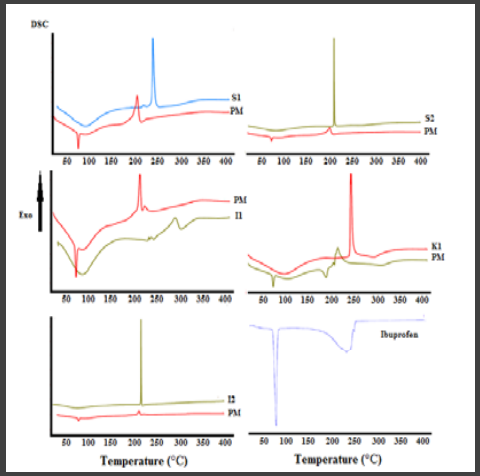
Results and Discussion

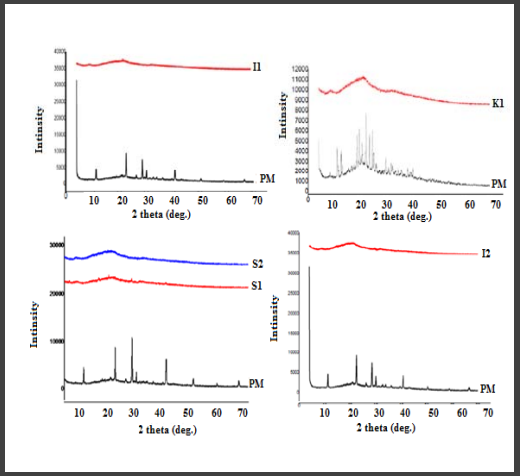
- **Ibuprofen was successfully loaded in the amorphous form inside the prepared carrier with a significant enhancement in the drug release profile.**







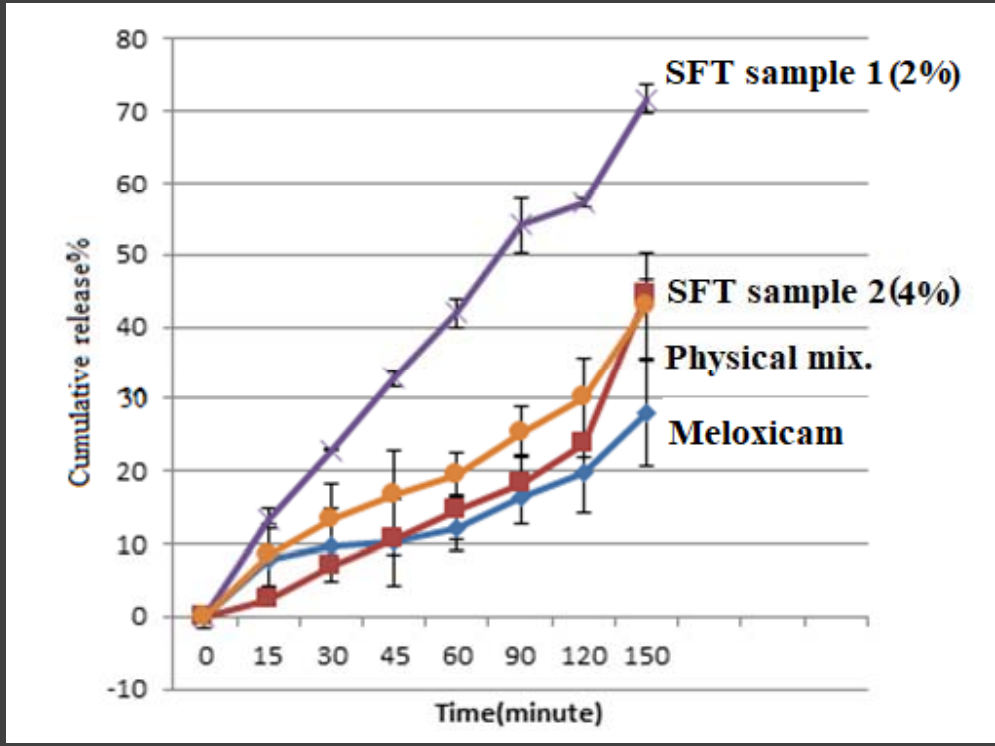




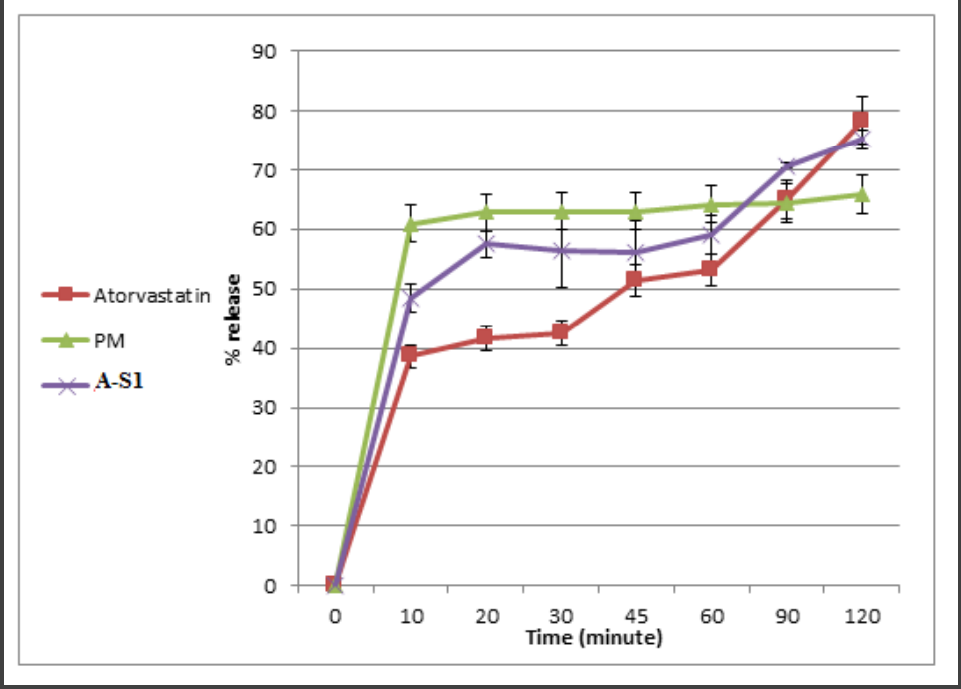
Investigation of Carrageenan Aerogels as a Potential Nanoporous Drug Carrier

- **The prepared Carrageenan microspherical aerogel carriers were successfully loaded with a model drug Ibuprofen, which was converted to a stable amorphous form inside, with an enhancement in the *in-vitro* release profile of the drug.**
- **Cross-linking agent can affect percentage of drug loading inside the microparticles.**
- **The stability of the loaded formulations affected by both: the polymer concentration and the Carrageenan type.**
- **Higher polymer concentration introduced more stabilization of the amorphous form.**

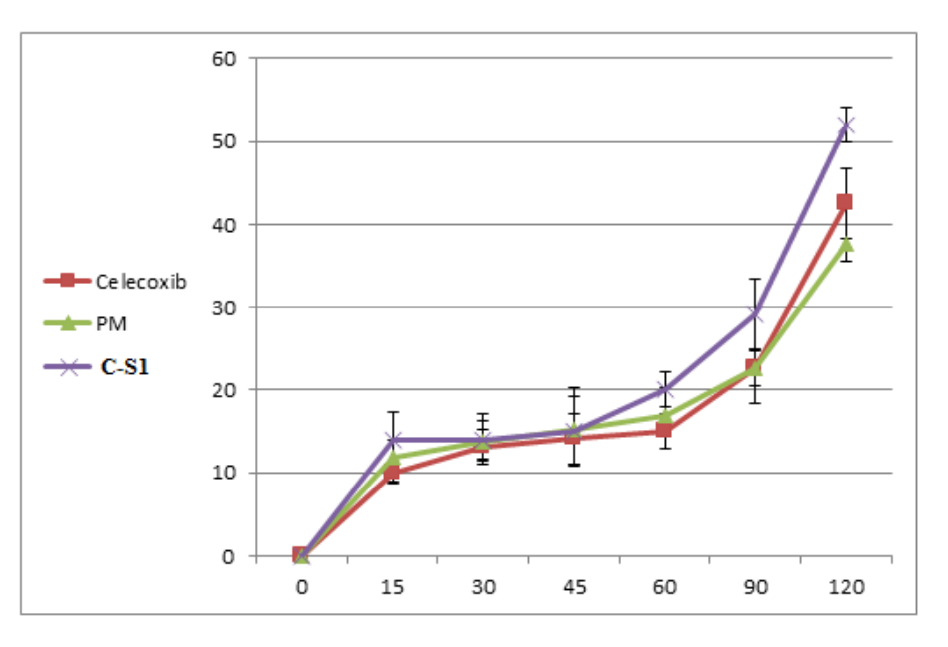
Meloxicam


80
70
60
50
40
30
20
10
0
-10
Cumulative release%
0
15
30
45
60
90
120
150
Time(minute)
SFT sample 1 (2%)
SFT sample 2 (4%)
Physical mix.
Meloxicam

Atorvastatin



Celecoxib



Remarks

- ✓Solid Dispersions
- ✓Complexation with Cyclodextrins
- ✓Aerogel Production

Limitations

- ❑ Cost.
- ❑ Scale-up.
- ❑ It is not a continuous Process.
- ❑ Physicochemical characterization of polymer and drugs under high pressure.

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