Influence of Progressive Change in the Degree of Saturation of API on the Performance of Topical Products

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Infinite Dose Permeation Studies

- No solvent Evaporation

Permeation rate and extent

α Drug concentration

α Thermodynamic activity

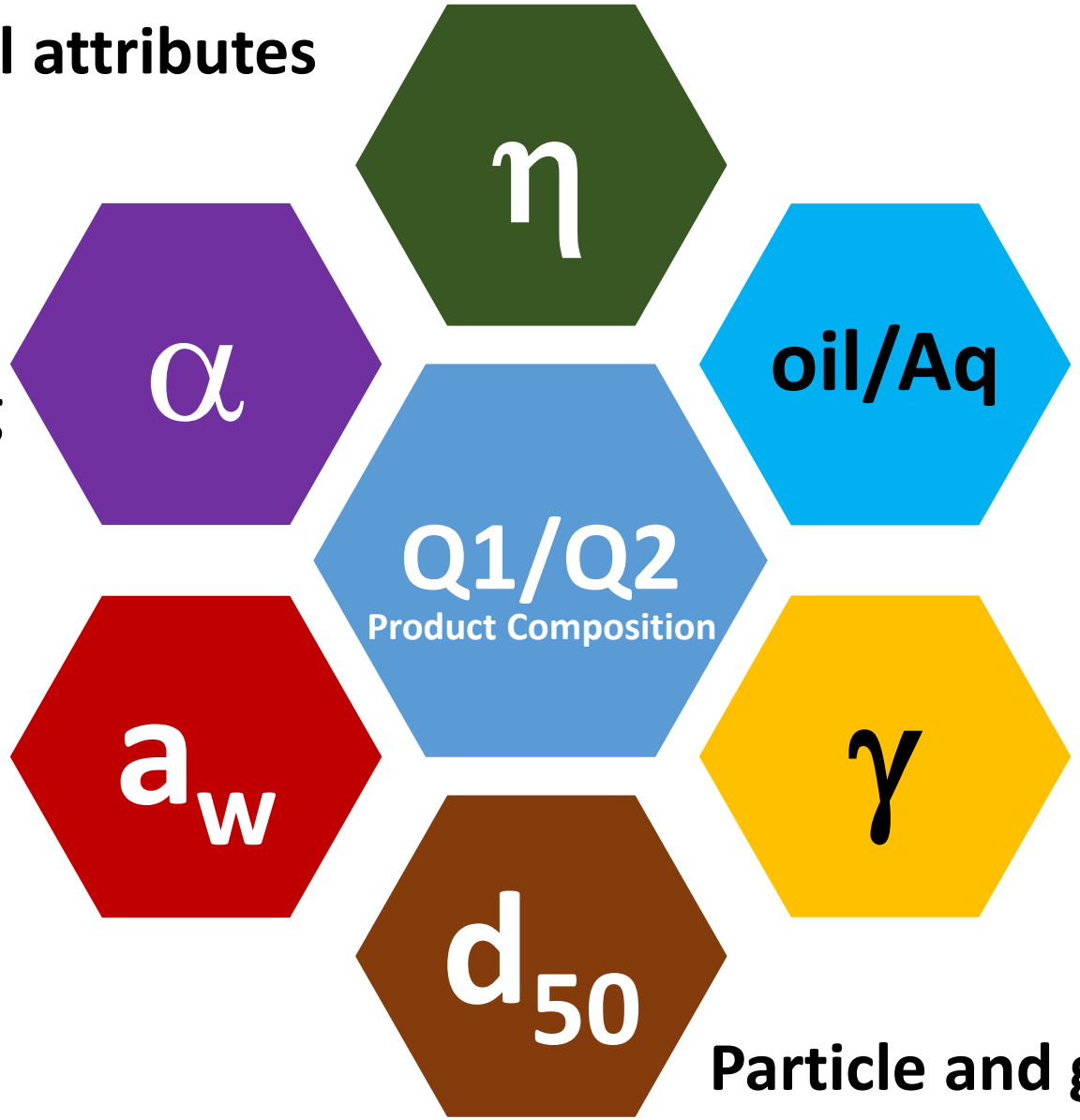
Degree of saturation (= Ratio of concentration of drug/saturation solubility)

Permeation rate and extent

α Degree of saturation

α Thermodynamic activity

Evaporative Metamorphosis in Topical Products



Rheological attributes

Drug Distribution

Thermodynamic activity of the drug

Adhesion to skin surface

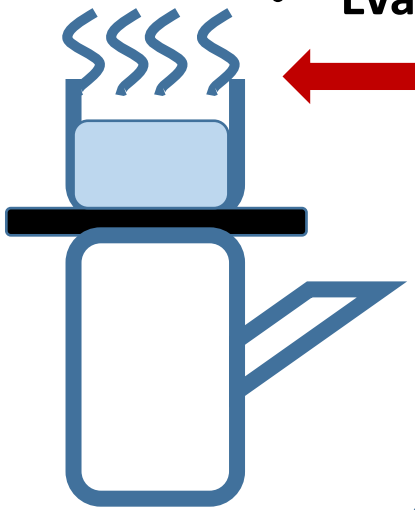
Water activity

Particle and globule sizes

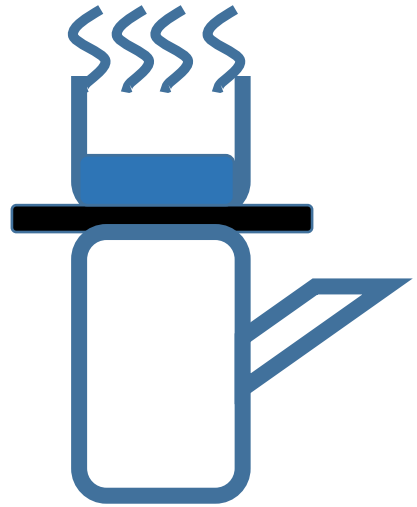
Finite Dose Studies-Single (Unary) Solvent system

- Evaporation

Open



Time



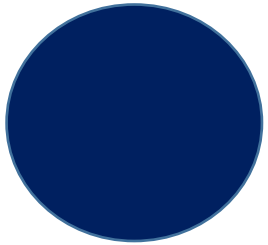
Solvent Evaporation

Increase in Drug concentration

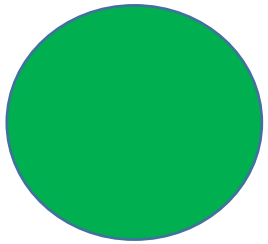
Increase in Degree of Saturation (Thermodynamic activity)

Rate of permeation of drug (Transdermal flux) α Rate of increase of Degree of saturation of the API

Binary Solvent System



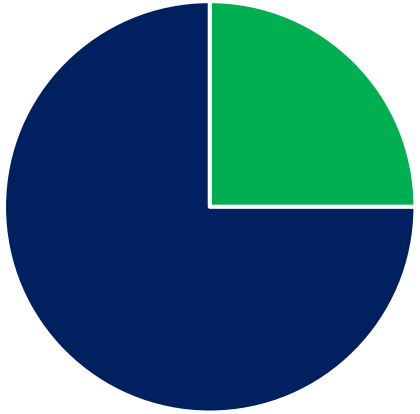
Solvent A
BP: 100^{O} C



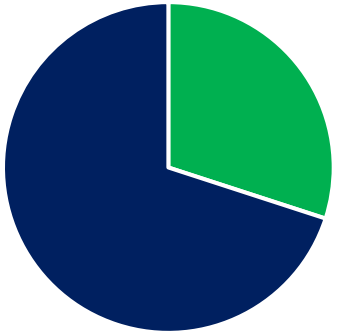
Solvent B
BP: 160^{O} C

Changing solvent mole fraction with time

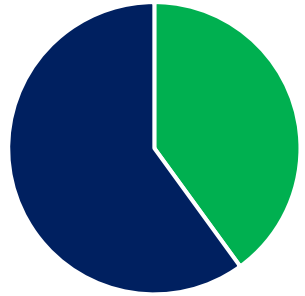
t0



t1



t2



Drug Concentration

Solubility

Degree of saturation

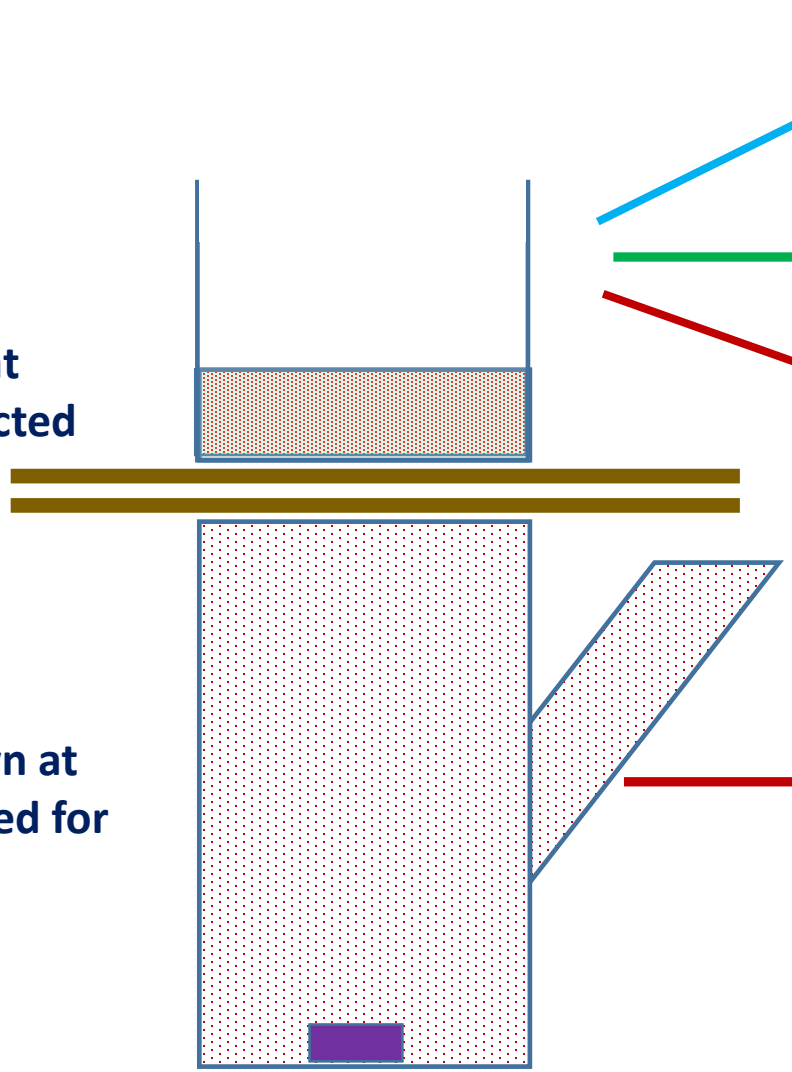
Semi-Infinite Dose IVPT-Experimental Design

Water
BP: 100^{O} C

PEG 200
BP: 160^{O} C

Donor samples were drawn at different time points and subjected for analysis

Receptor samples were drawn at same time points and subjected for analysis



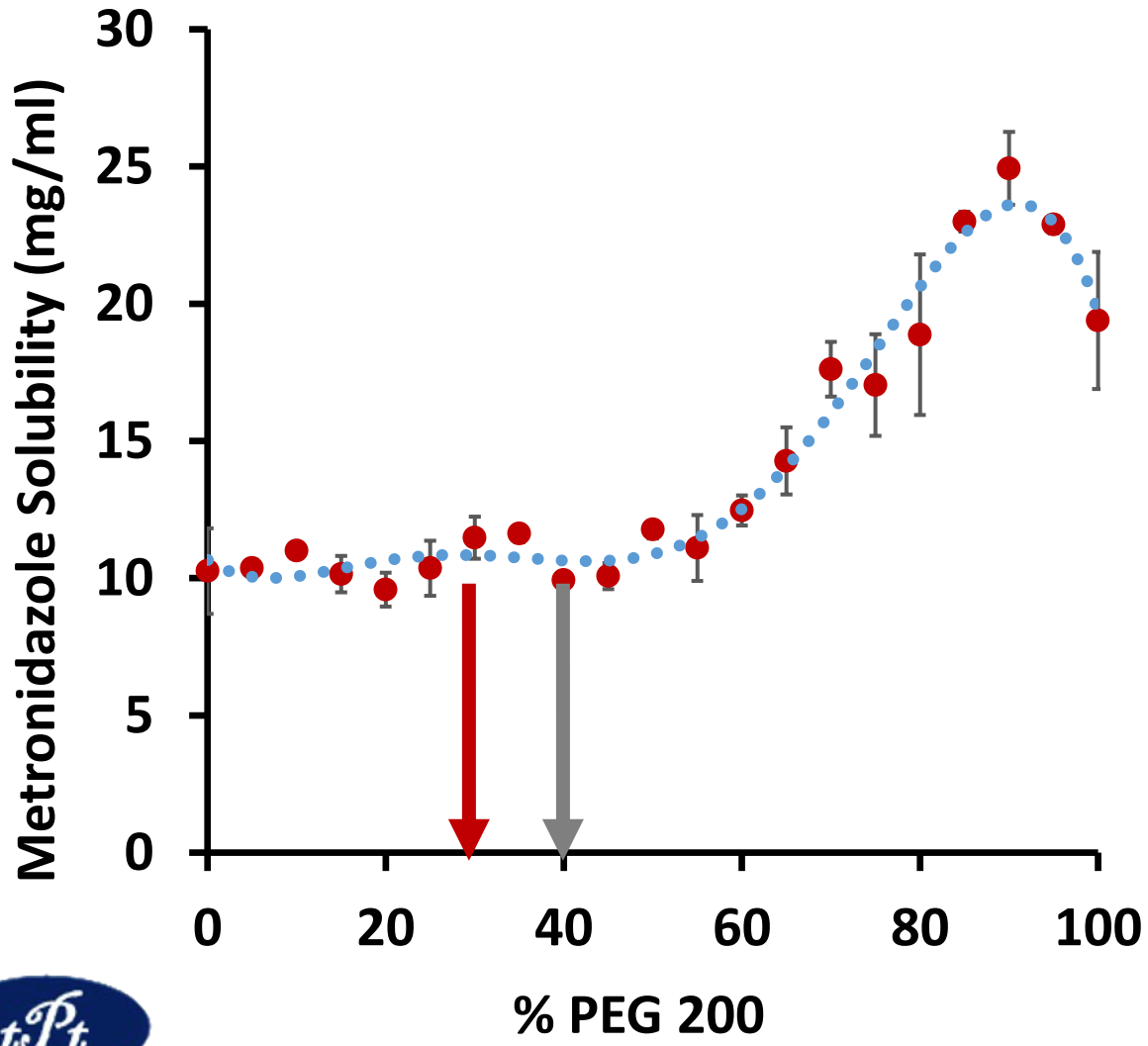
Water Content

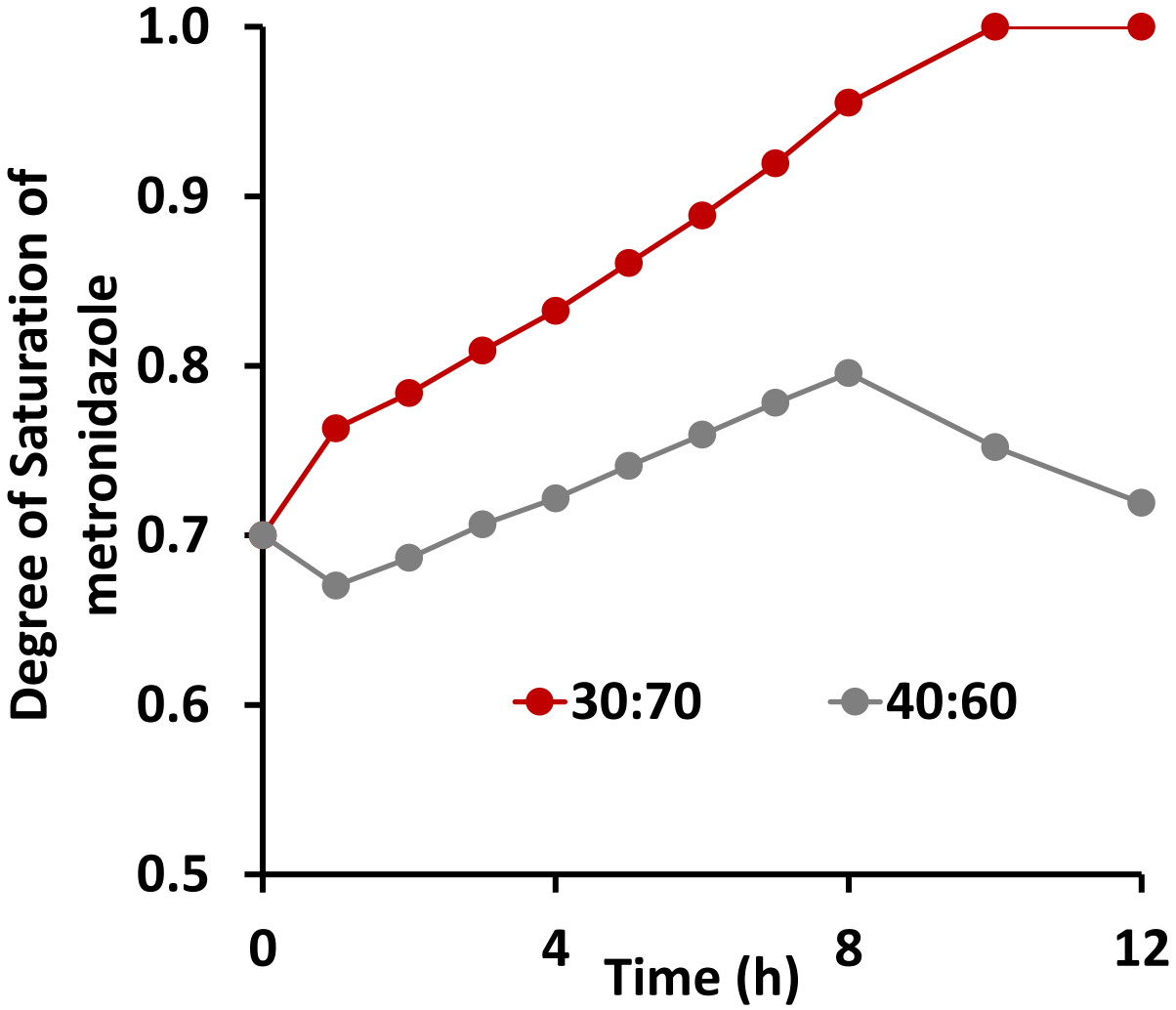
PEG 200 Analysis

Drug concentration

Drug concentration

Solubility of Metronidazole in PEG 200 : Water binary solvent system



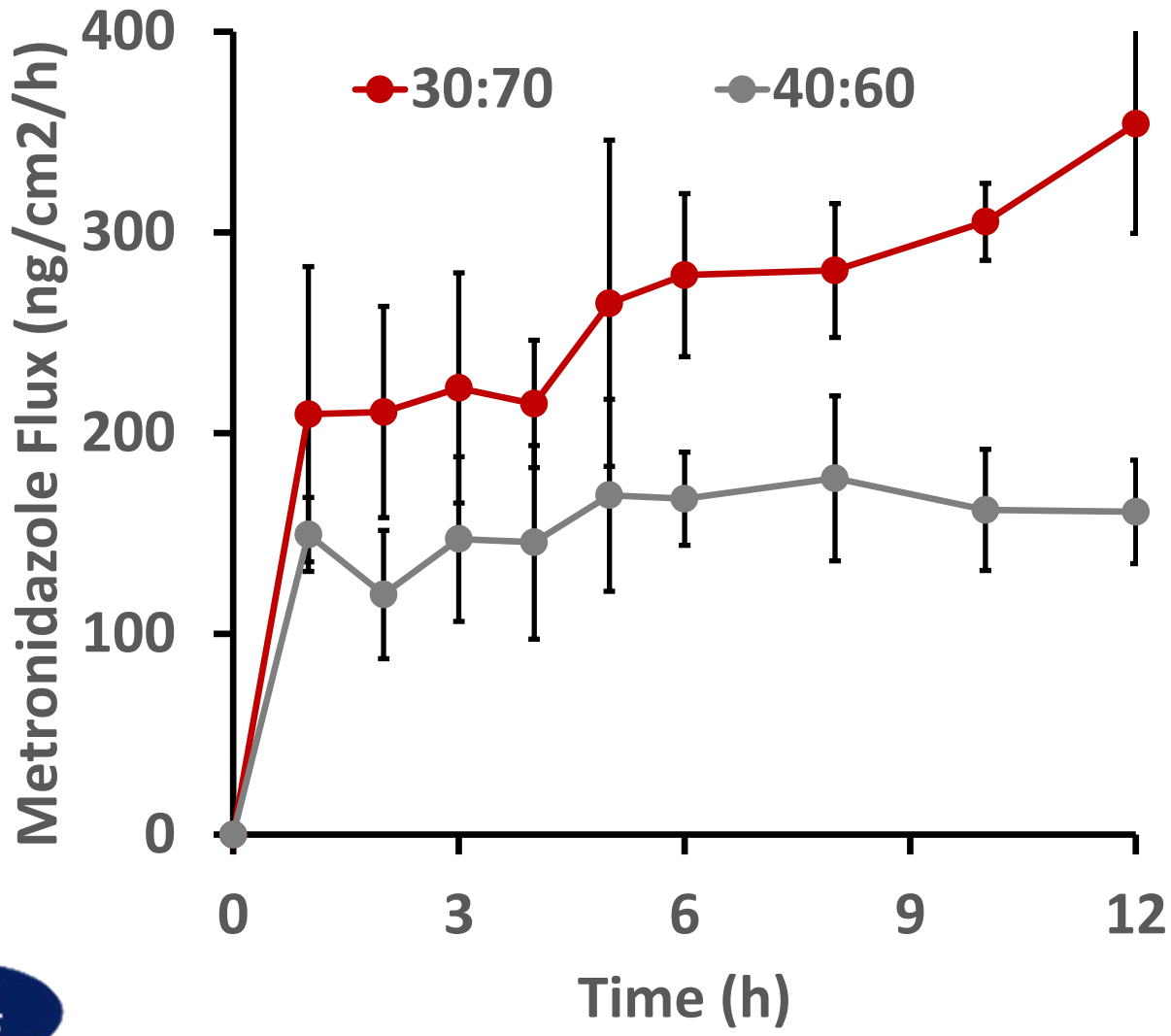


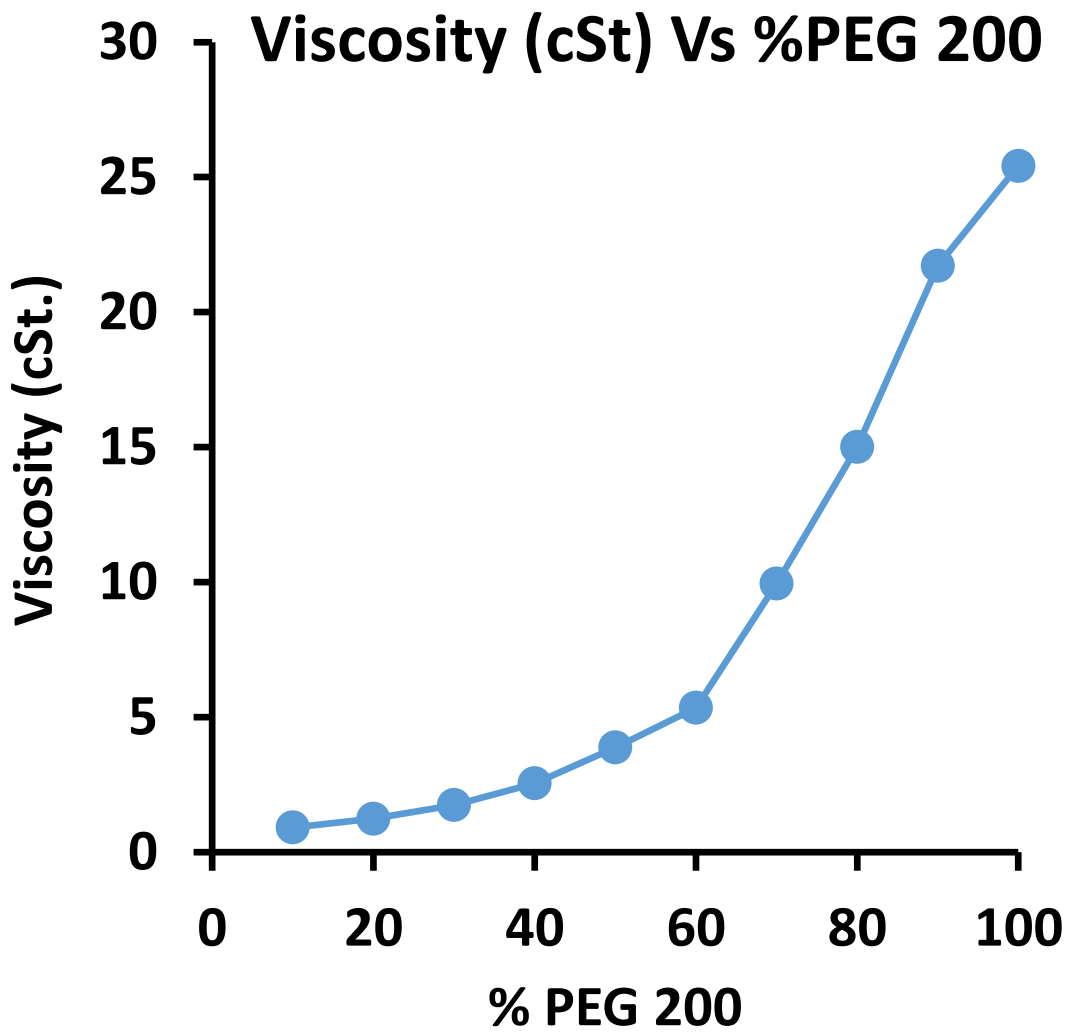
Change in degree of saturation (α) of metronidazole PEG 200 : Water binary solvent system

Time (h)	30:70				40:60			
	PEG (%w/w)	Solubility (mg/mL	Drug Conc. (mg/mL)	α	PEG (%w/w)	Solubility (mg/mL	Drug Conc. (mg/mL)	α
0	30	11.48	8.04	0.70	40	9.93	6.95	0.70
1	30.31	10.84	8.27	0.76	41.33	10.63	7.12	0.67
2	30.85	10.83	8.49	0.78	42.48	10.62	7.29	0.69
3	31.26	10.83	8.76	0.81	42.92	10.62	7.50	0.71
4	32.21	10.81	9.00	0.83	43.79	10.62	7.67	0.72
5	33.03	10.79	9.29	0.86	44.82	10.64	7.88	0.74
6	33.72	10.78	9.58	0.89	45.7	10.66	8.09	0.76
7	34.82	10.75	9.89	0.92	46.74	10.69	8.32	0.78
8	36.22	10.72	10.24	0.96	48.23	10.76	8.56	0.80
10	39.32	10.65	10.65	1.00	58.35	12.12	9.12	0.75
12	41.18	10.63	10.63	1.00	62.15	13.12	9.43	0.72

In vitro Permeation Profile of Metronidazole

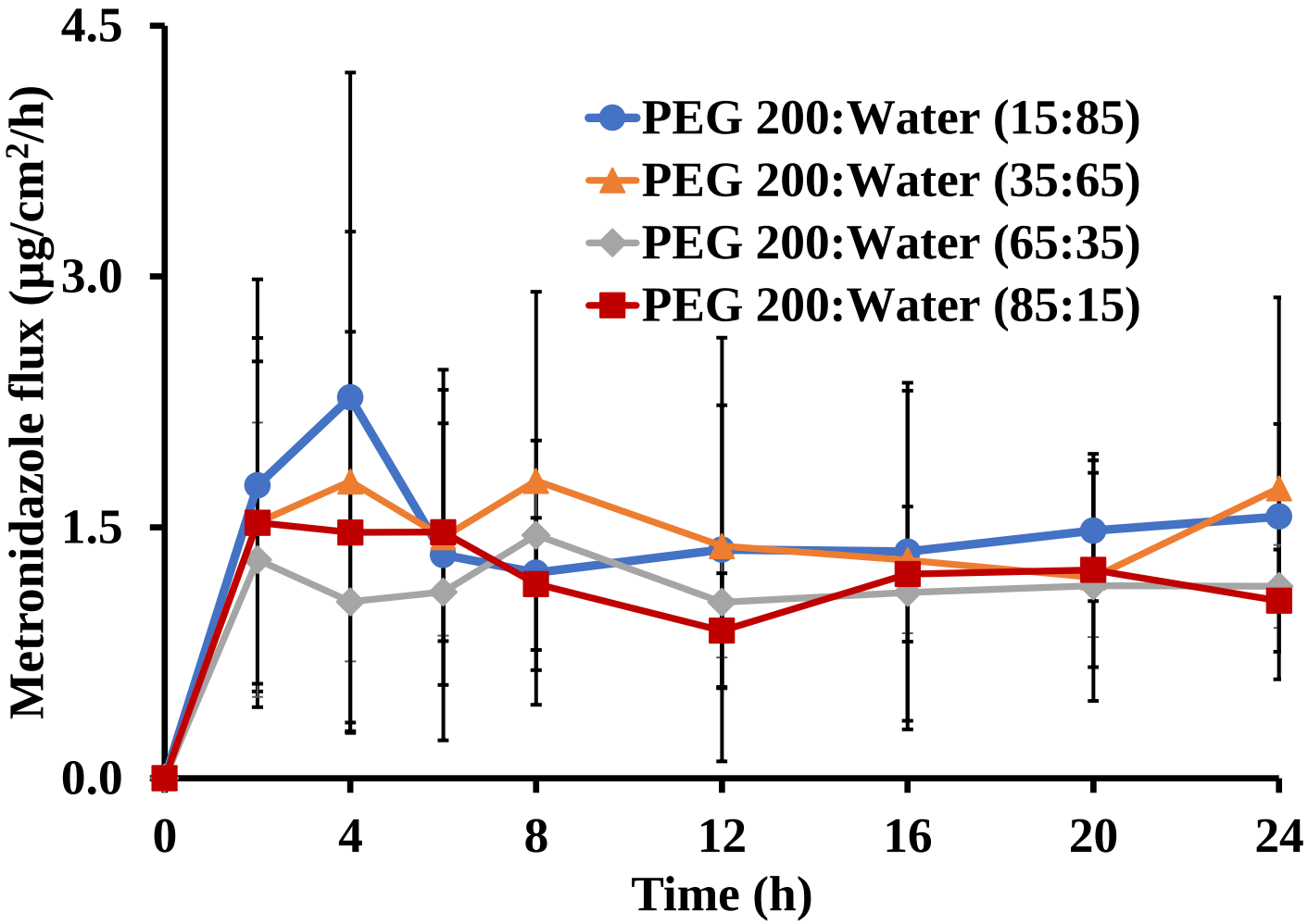
PEG 200-water solutions (α=0.7)





Permeation profile of metronidazole from PEG-water system at same degree of saturation (α=0.5) (Infinite Dose)

Metronidazole (α = 0.5)	
PEG 200:Water	Viscosity (cps.)
15:85	1.09
35:65	1.49
50:50	4.05
65:35	8.55
85:15	17.55



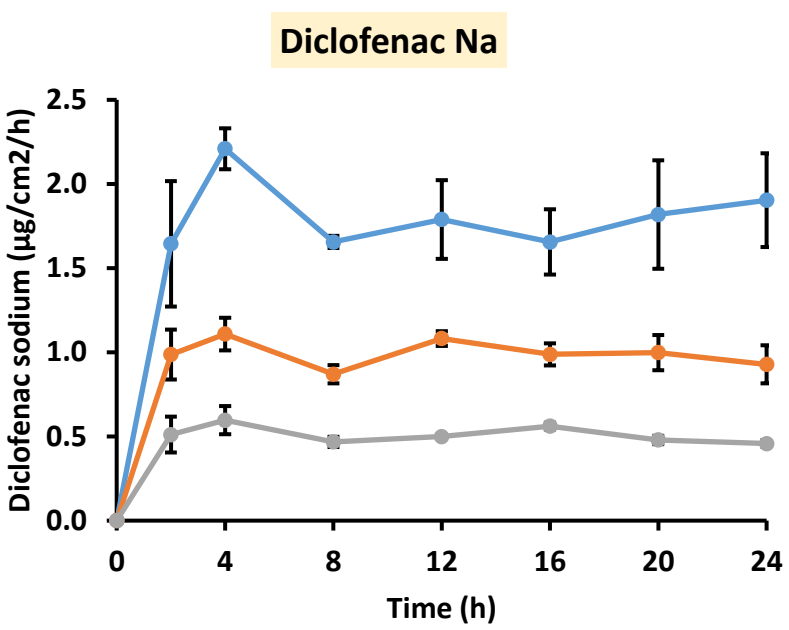
Composition	F1	F2	F3
PEG 200	1	10	20
EDTA	0.01	0.01	0.01
Sodium benzoate	0.02	0.02	0.02
Hydroxy ethyl cellulose	5	5	5
Water qs	100	100	100
API	0.5	0.5	0.5

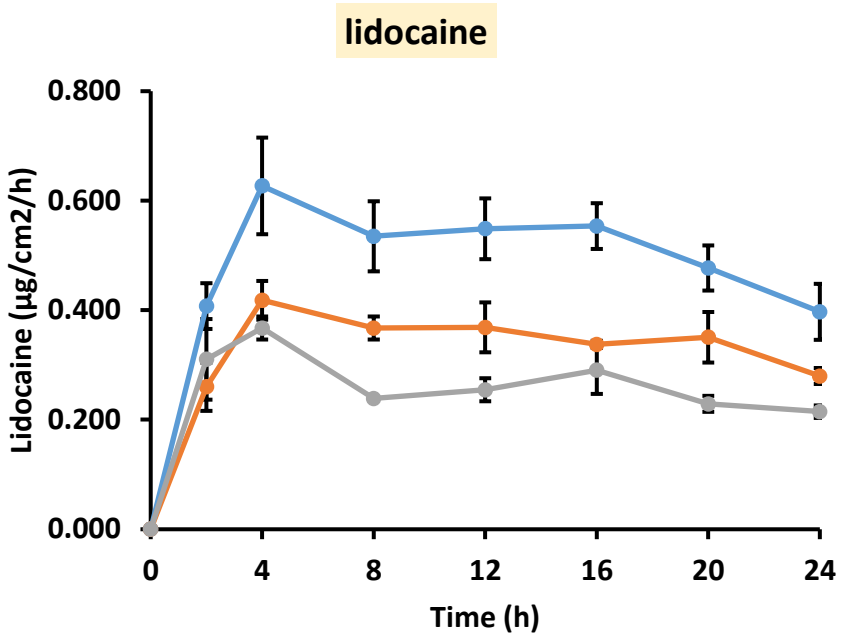
PEG-200	1	10	20
Metronidazole	0.5	0.5	0.5
Solubility	10.3	10.7	11
Degree of Saturation at 0.5%	0.49	0.45	0.51
Viscosity	1950	2159.1	2027.9
pH	7.044 ± 0.009	7.026 ± 0.006	6.981± 0.010

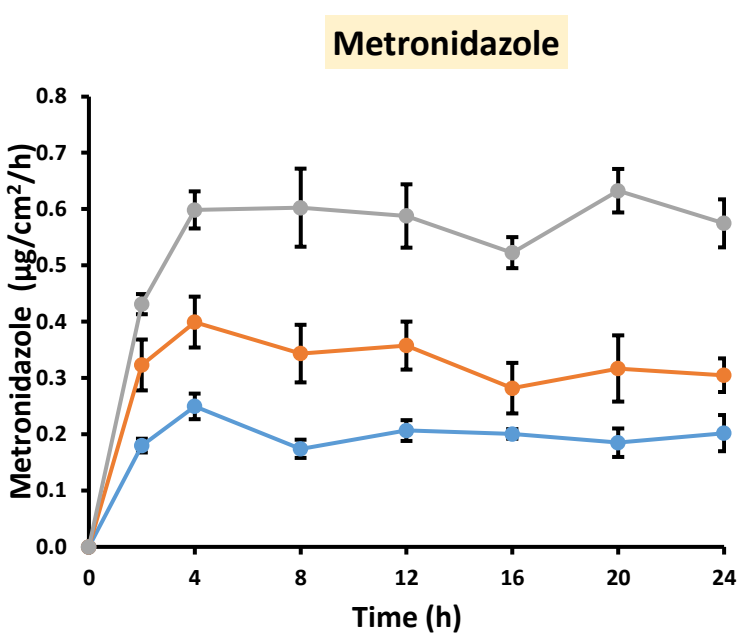
PEG-200	1	10	20
Diclofenac Na	0.5	0.5	0.5
Solubility	18	36.39	62.64
Degree of Saturation at 0.5%	0.28	0.14	0.08
Viscosity	388.49	614.62	1099.1
pH	7.8 ± 0.03	7.6± 0.03	7.3 ± 0.01

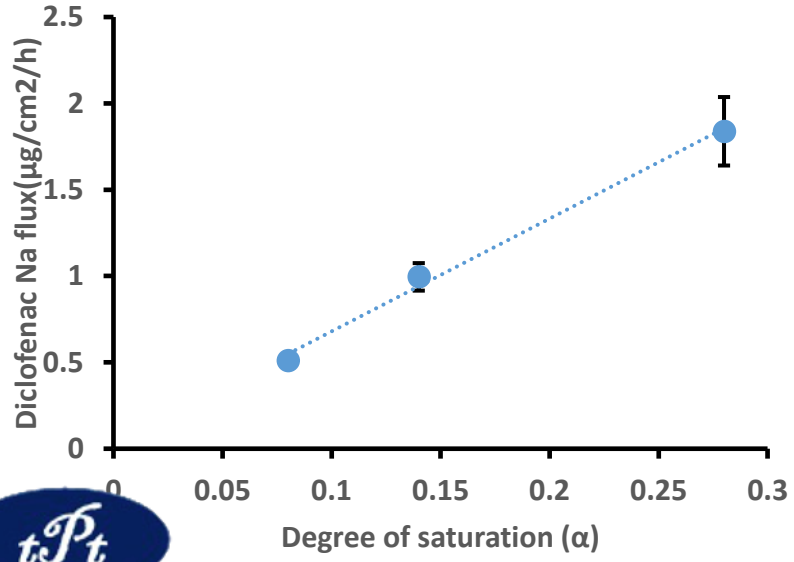
PEG-200	1	10	20
Lidocaine	0.25	0.25	0.25
Solubility	4.2	5.3	5.95
Degree of Saturation at 0.25%	0.6	0.47	0.42
Viscosity	2074.6	1927.9	2139
pH	8.460 ± 0.042	8.654 ± 0.104	8.624 ± 0.056

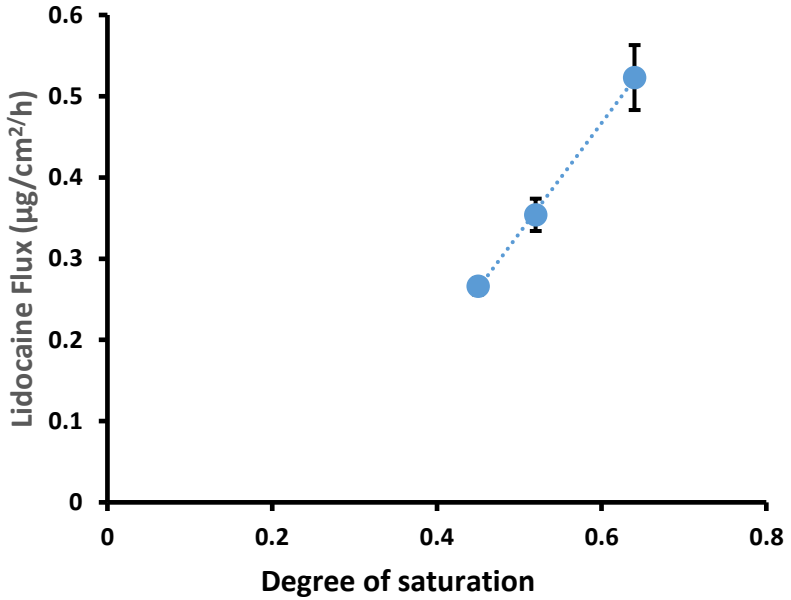
Infinite dose IVPT studies of topical gels (n=3 ± SEM)

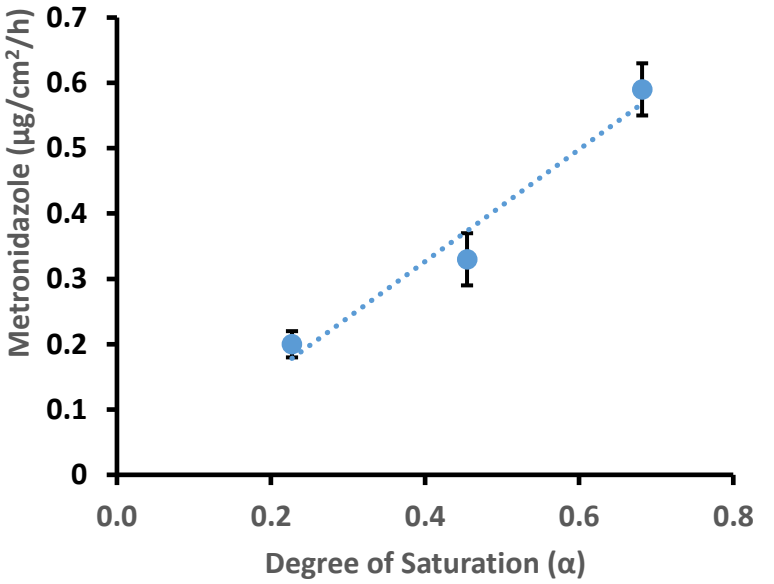




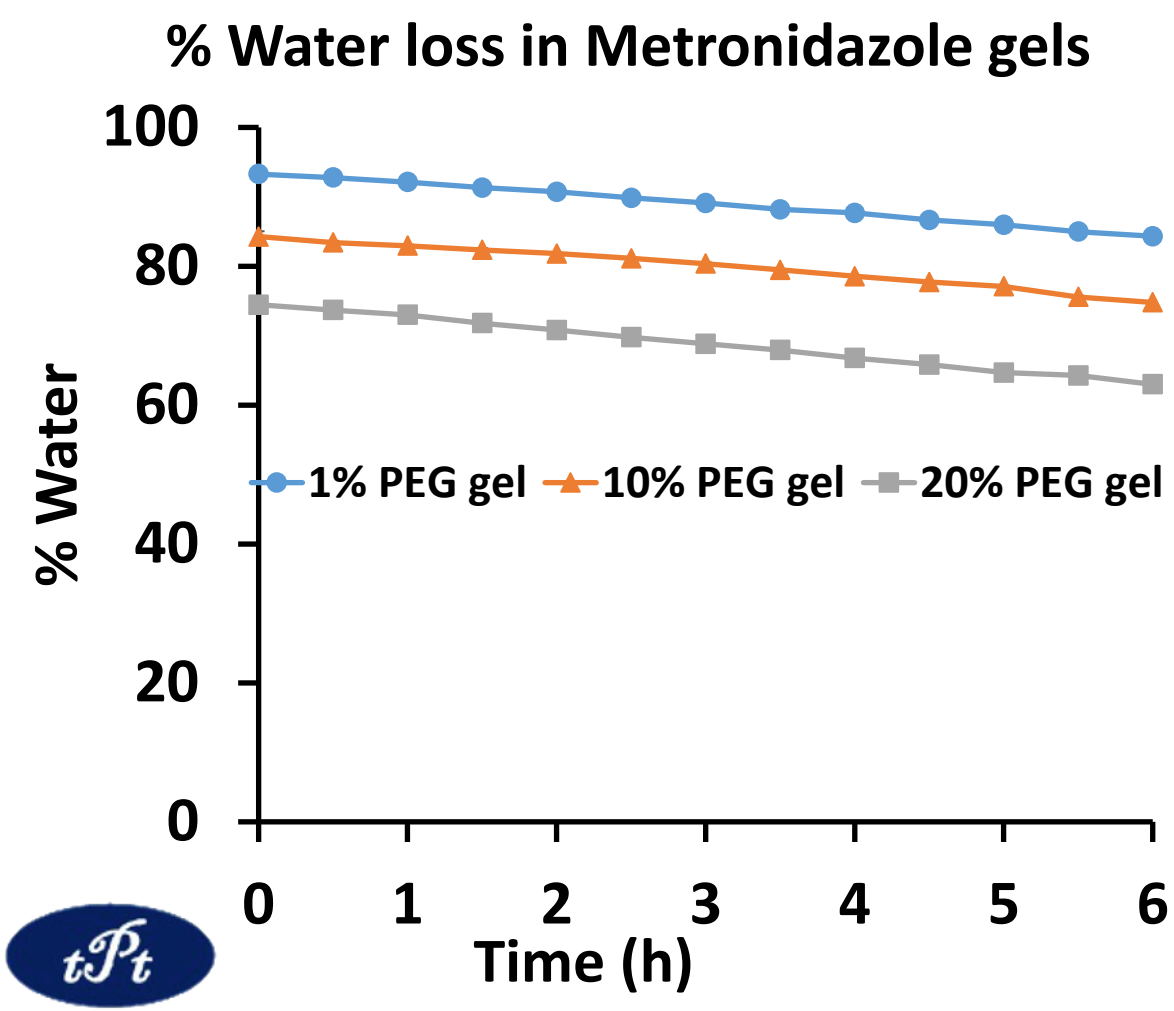


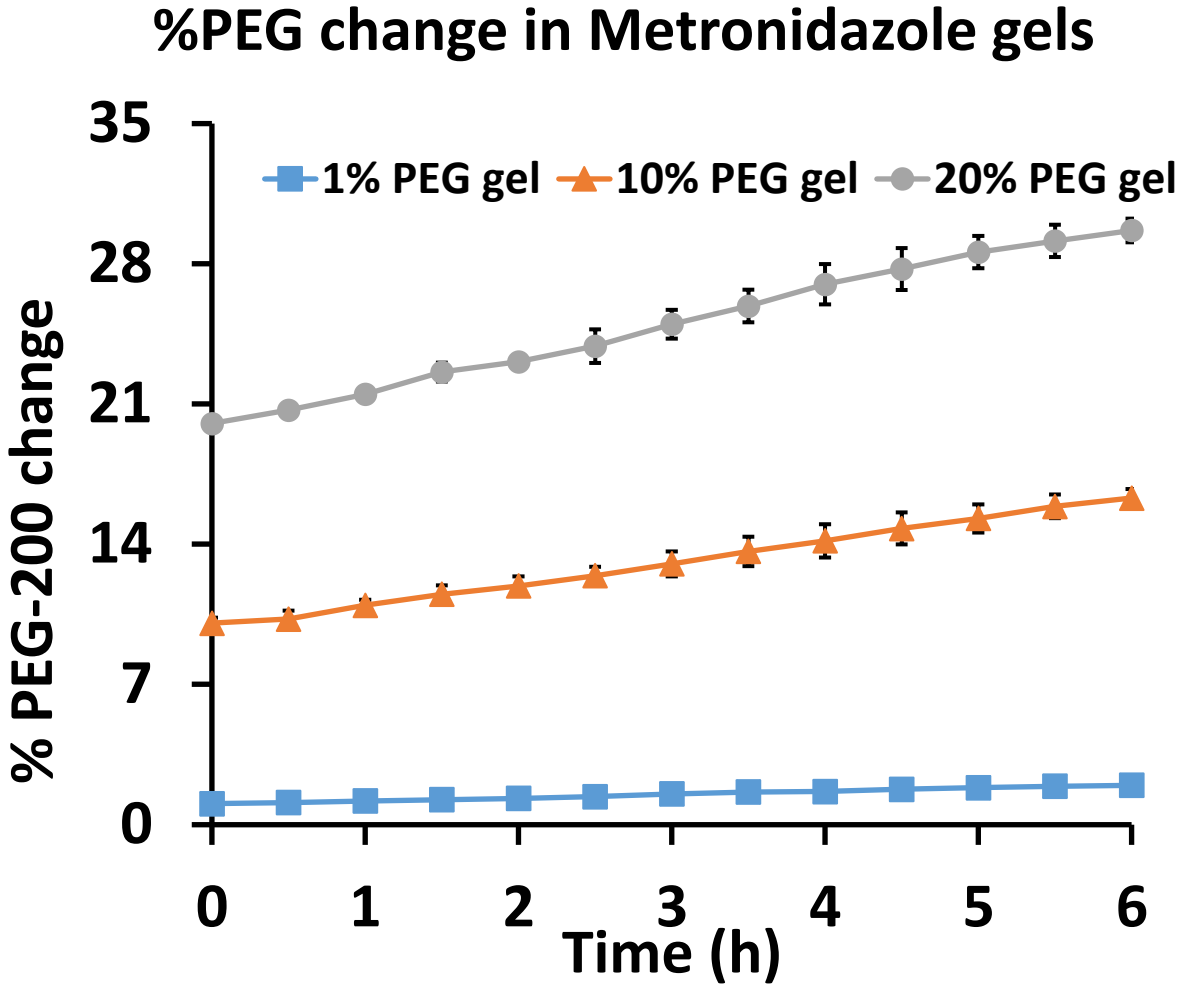




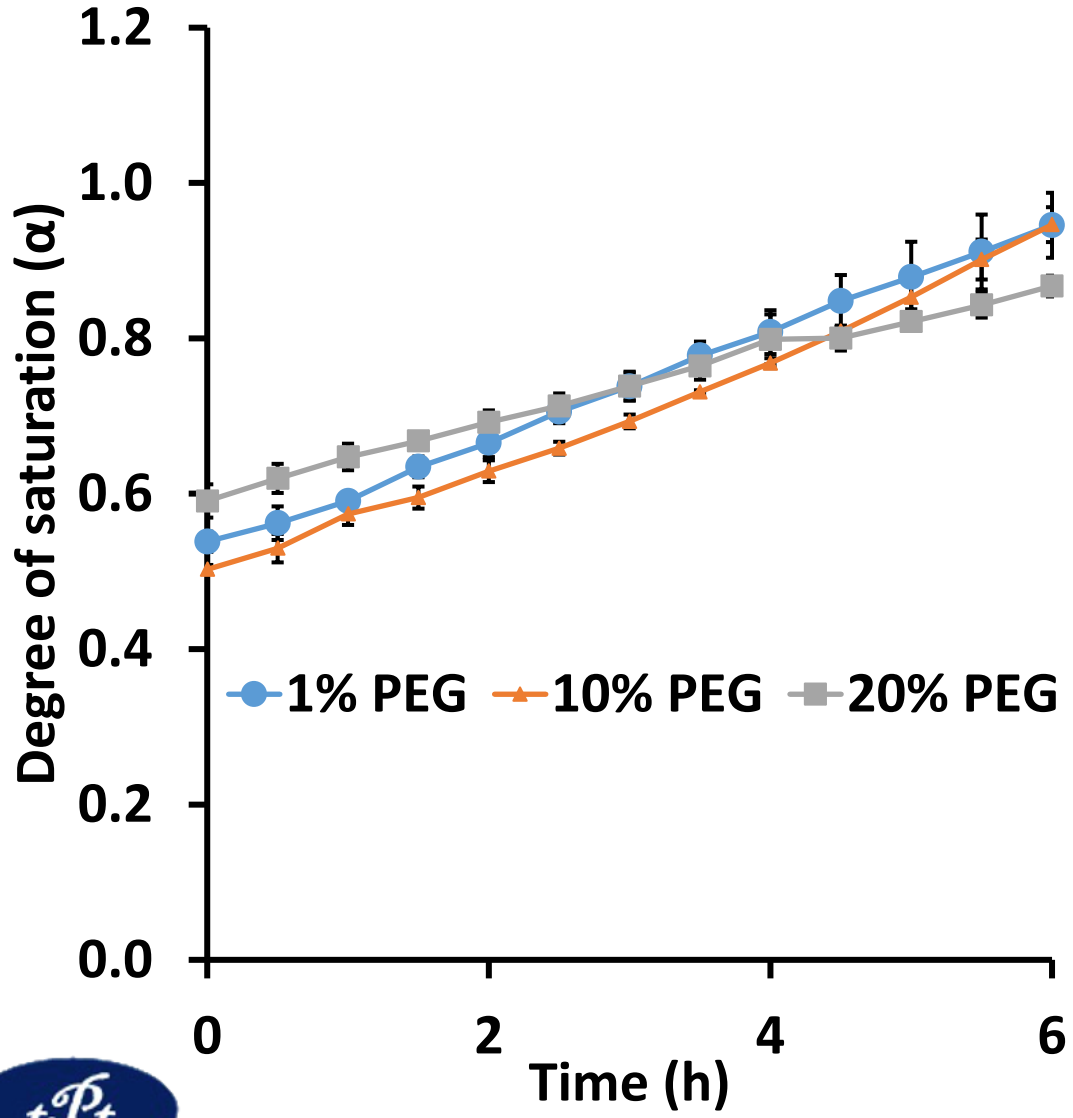


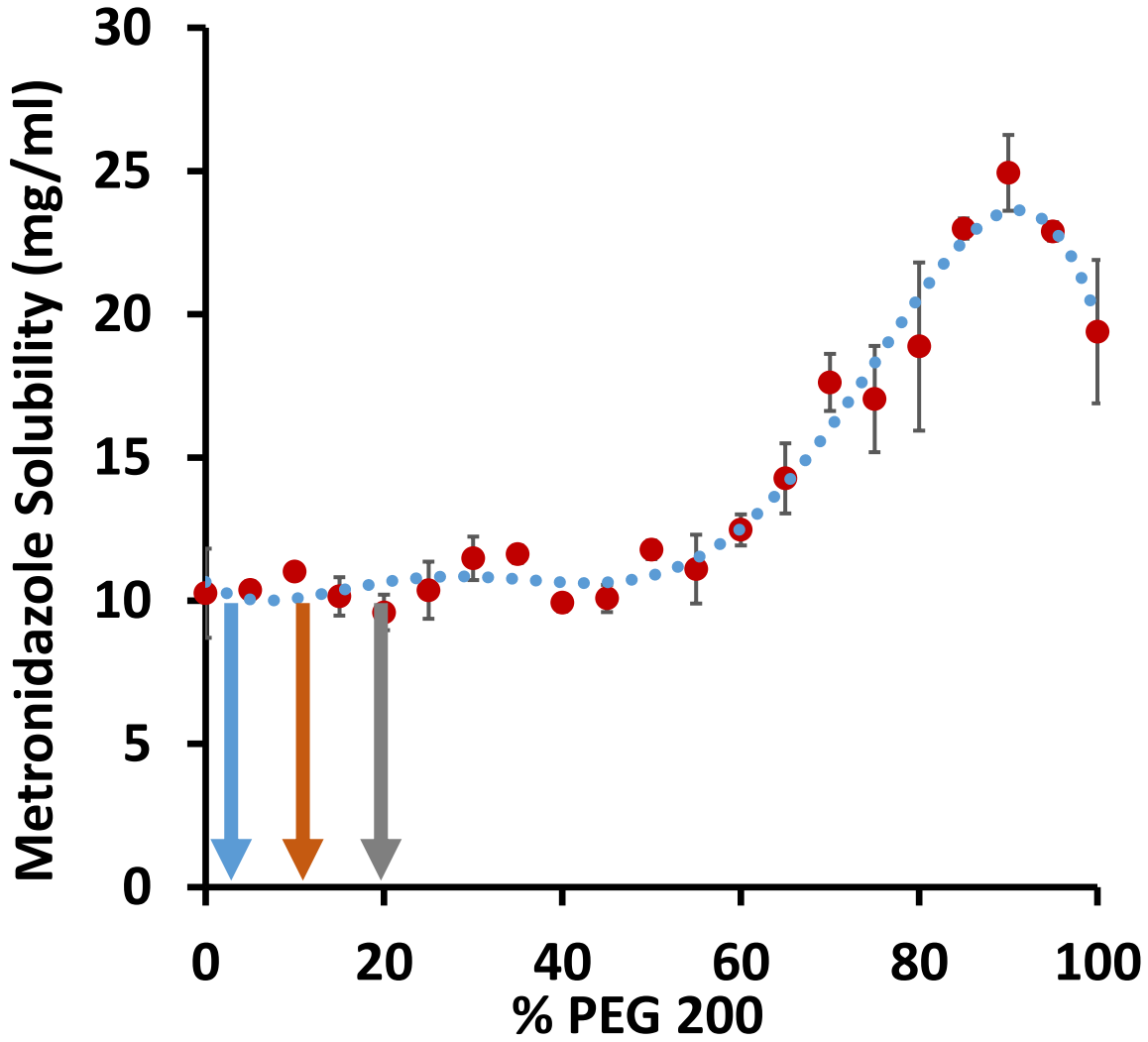
Time course of Water & PEG-200 concentration in Metronidazole Gels (Semi-infinite dose)



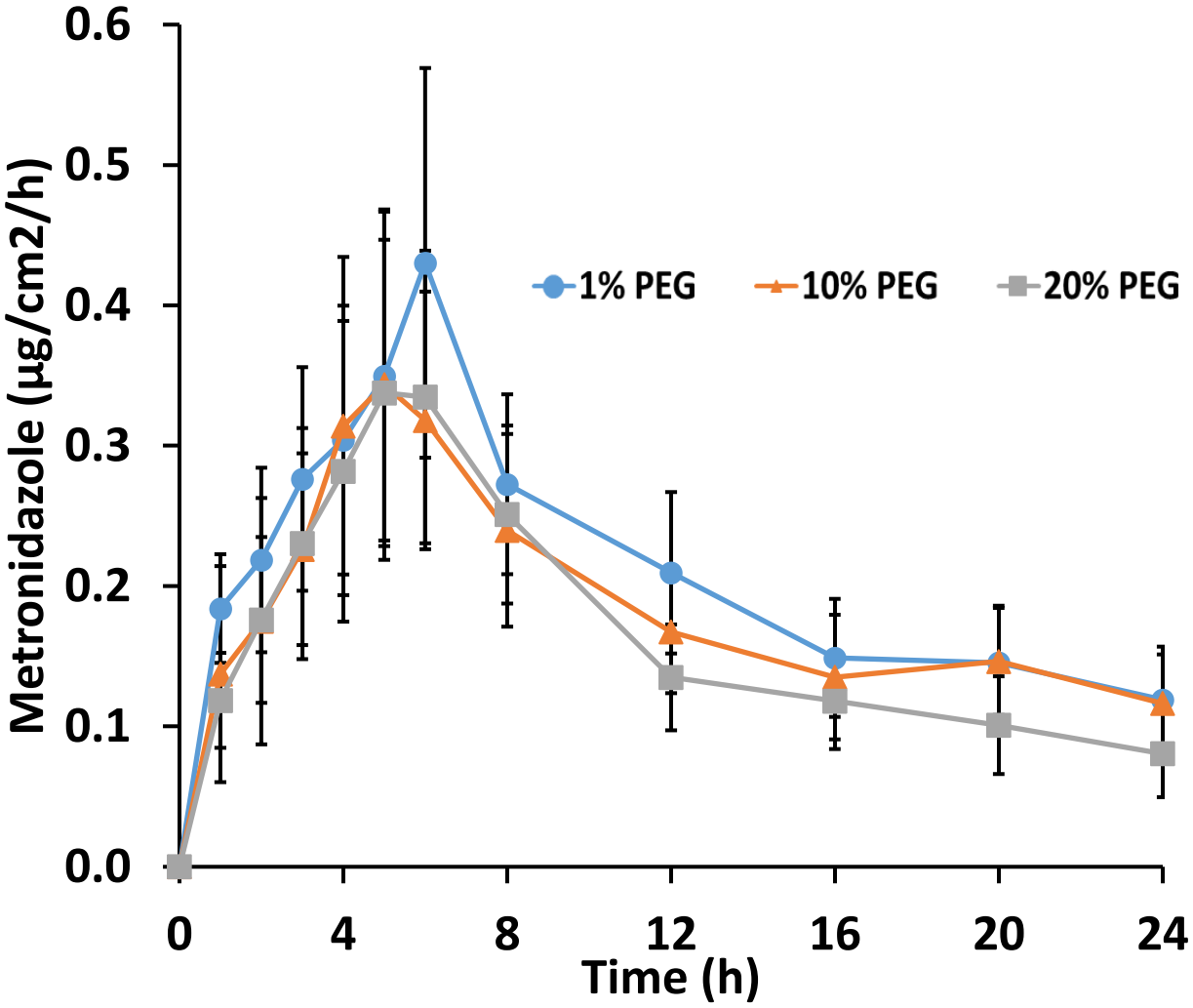


Time course of DOS of Metronidazole (Semi-finite dose, n=3 ± SEM)



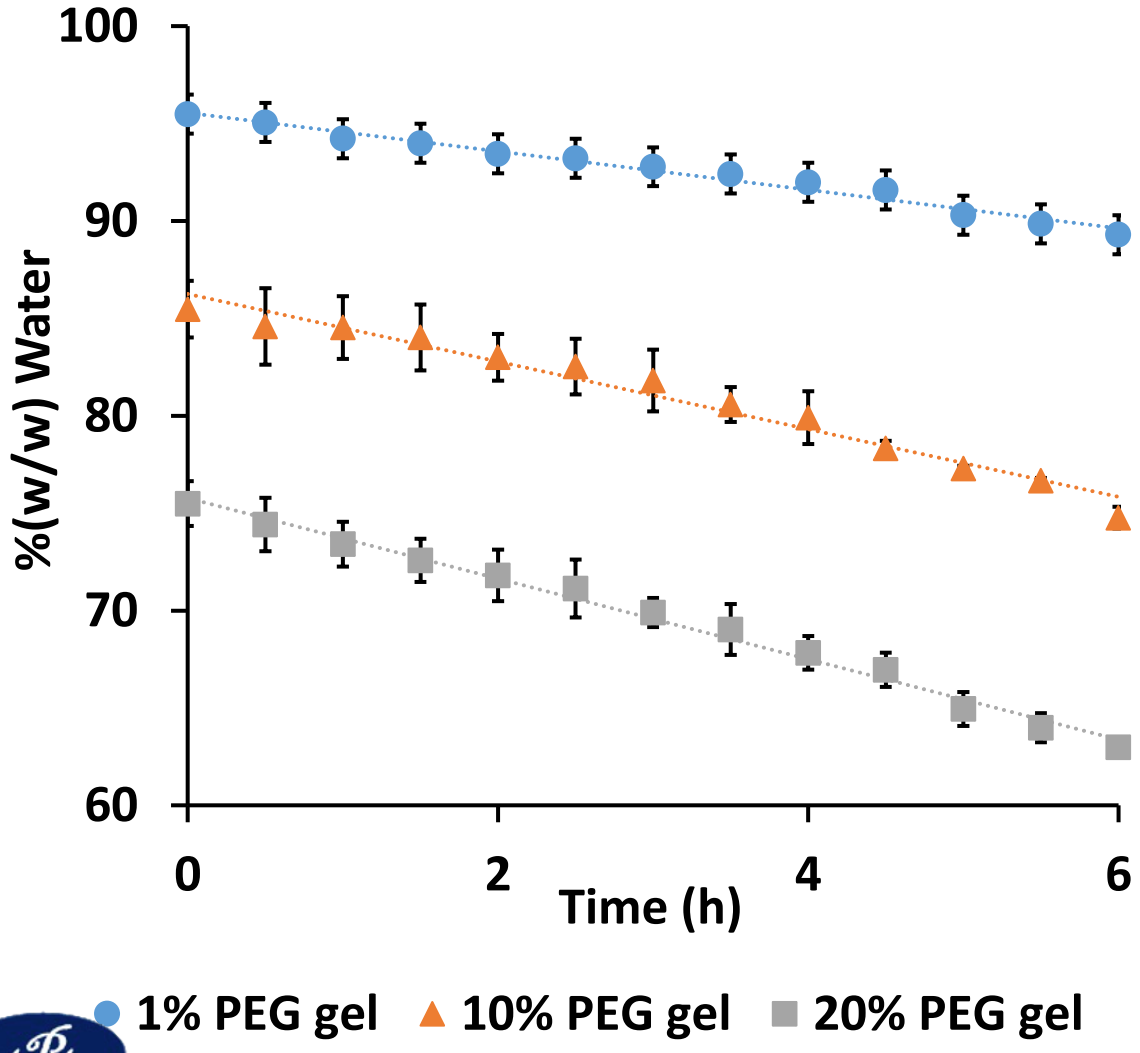


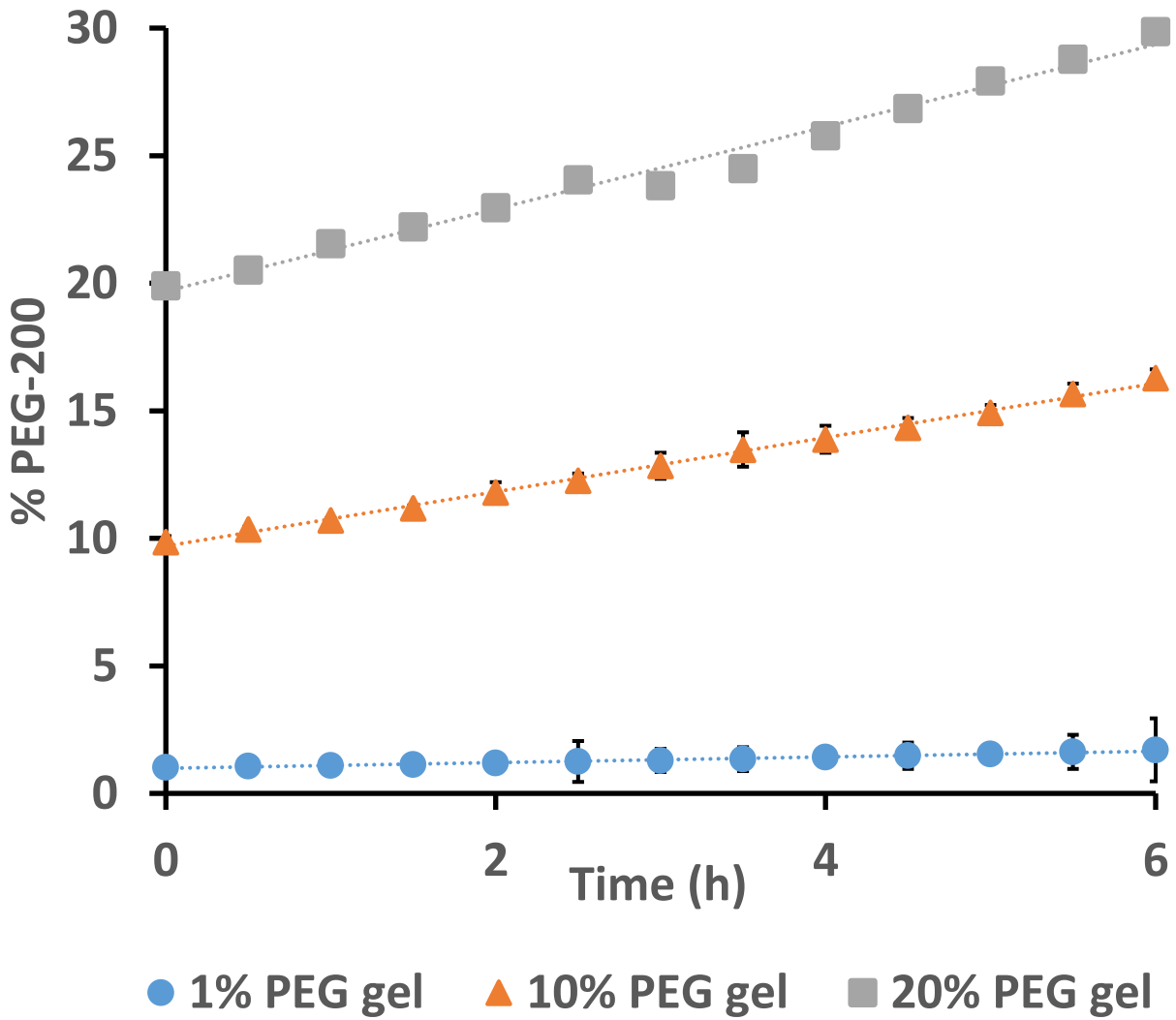
Permeation Flux profile of Metronidazole Gels (Semi-infinite dose, n=3 ± SEM)



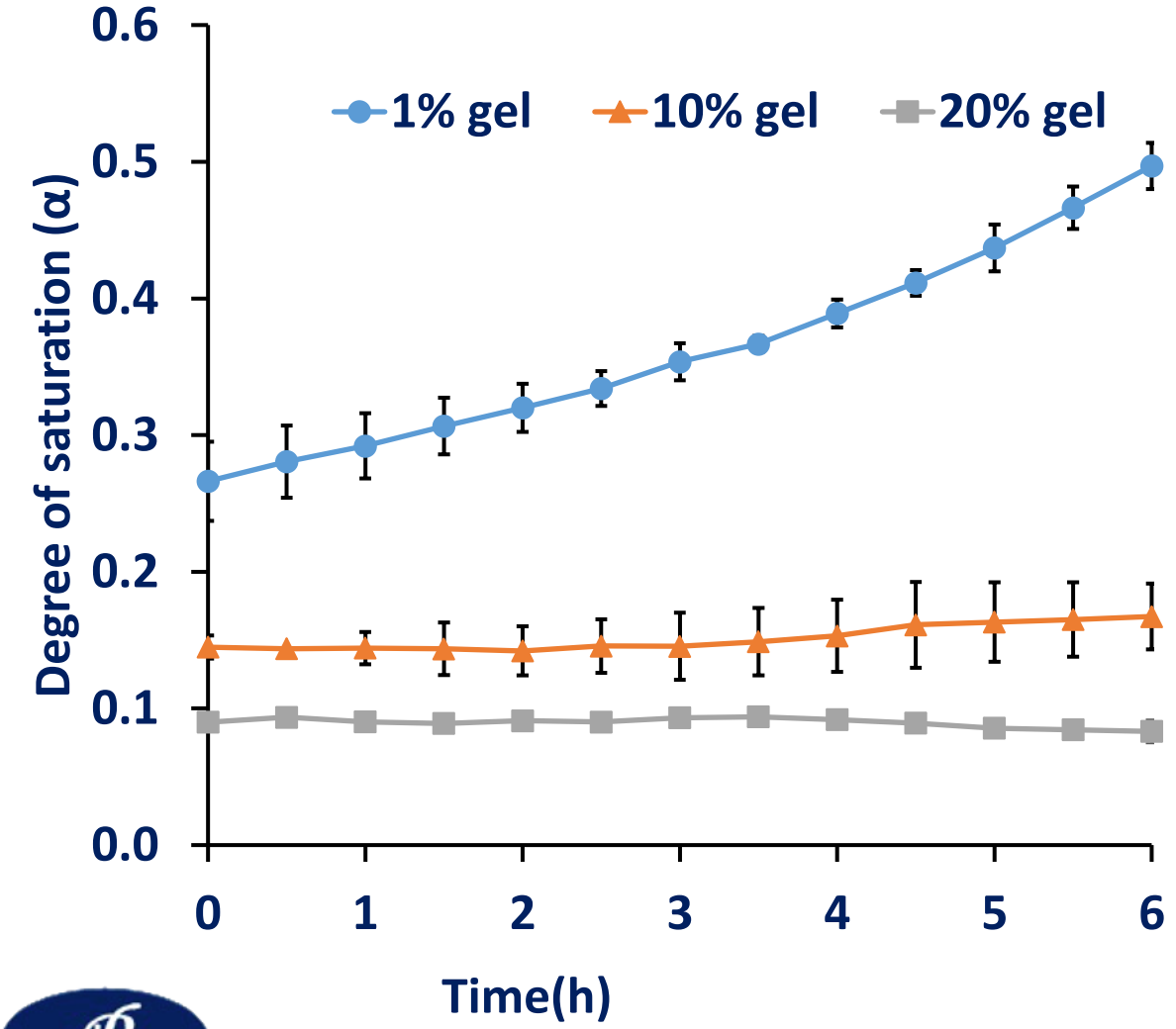
Gel	AUC (µg/cm²)	Jmax (µg/cm²/h)	Tmax (h)
1% PEG 200	5.05 ± 1.30	0.97 ± 0.22	12.00 ± 0.00
10% PEG 200	5.42 ± 1.34	0.81 ± 0.72	12.00 ± 0.00
20% PEG 200	3.98 ± 1.16	0.77 ± 0.19	12.00 ± 0.00

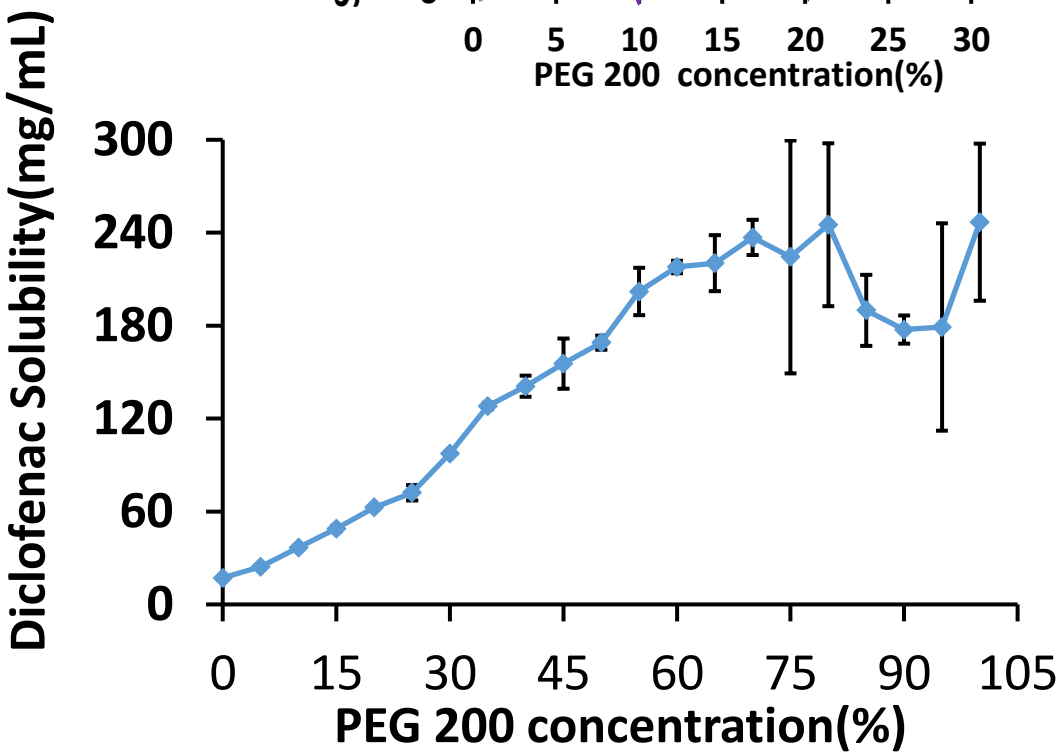
Time course of Water & PEG-200 concentration in Diclofenac Gels (Semi-infinite dose)

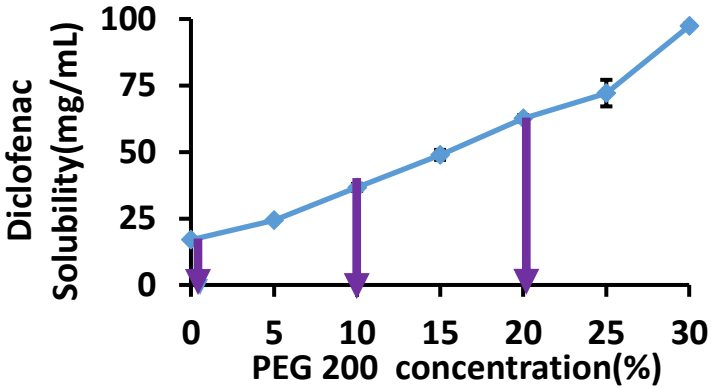




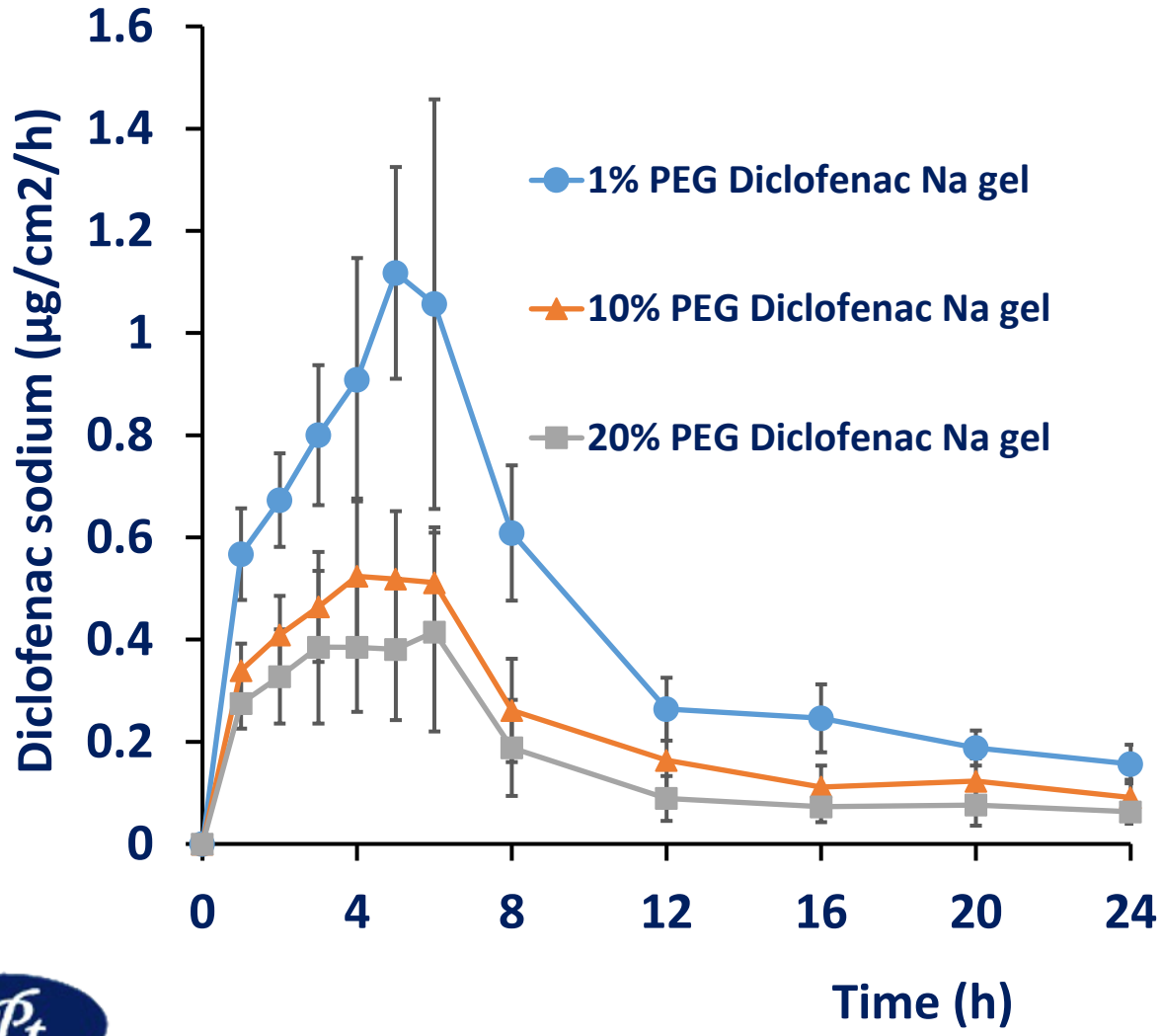
Degree of saturation profile of Diclofenac Gels (Semi-finite dose, n=3 ± SEM)





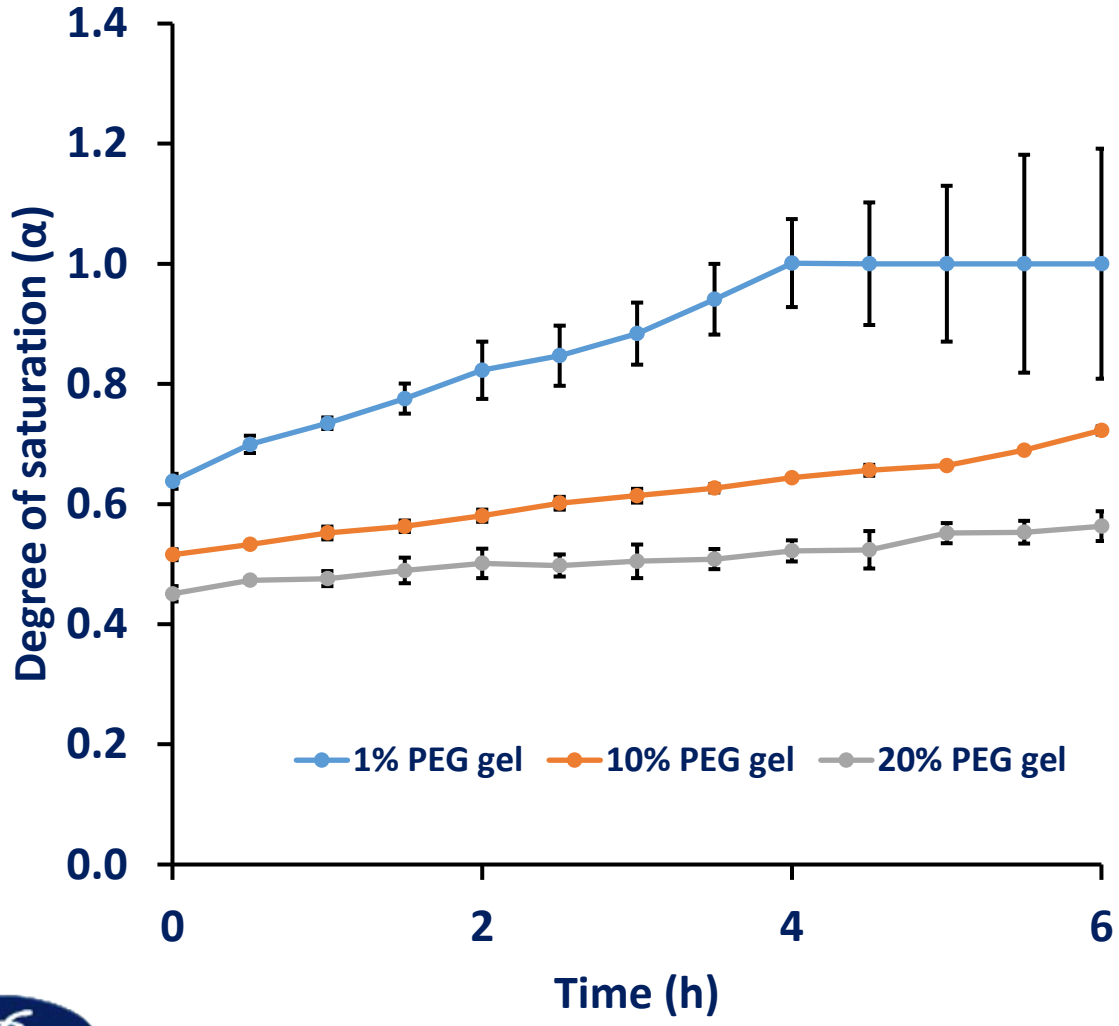


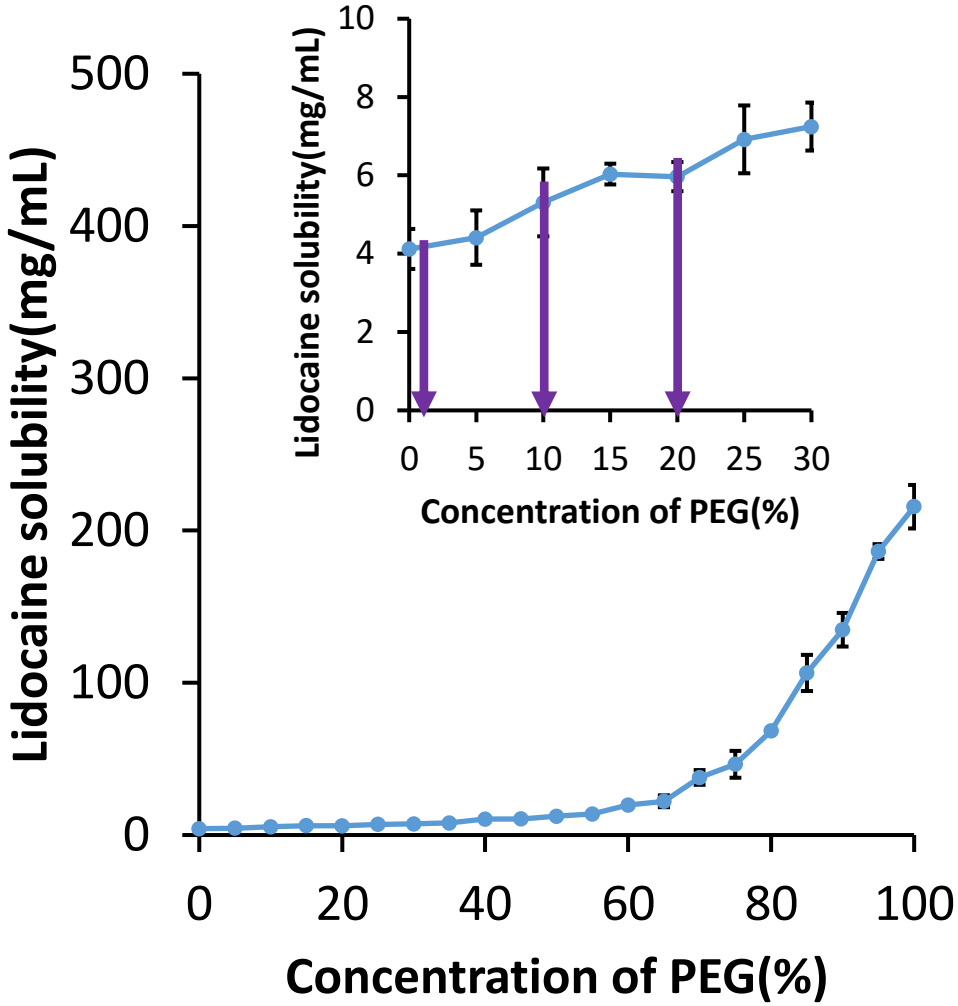
Permeation Flux profile of Diclofenac Gels (Semi-finite dose, n=3 ± SEM)



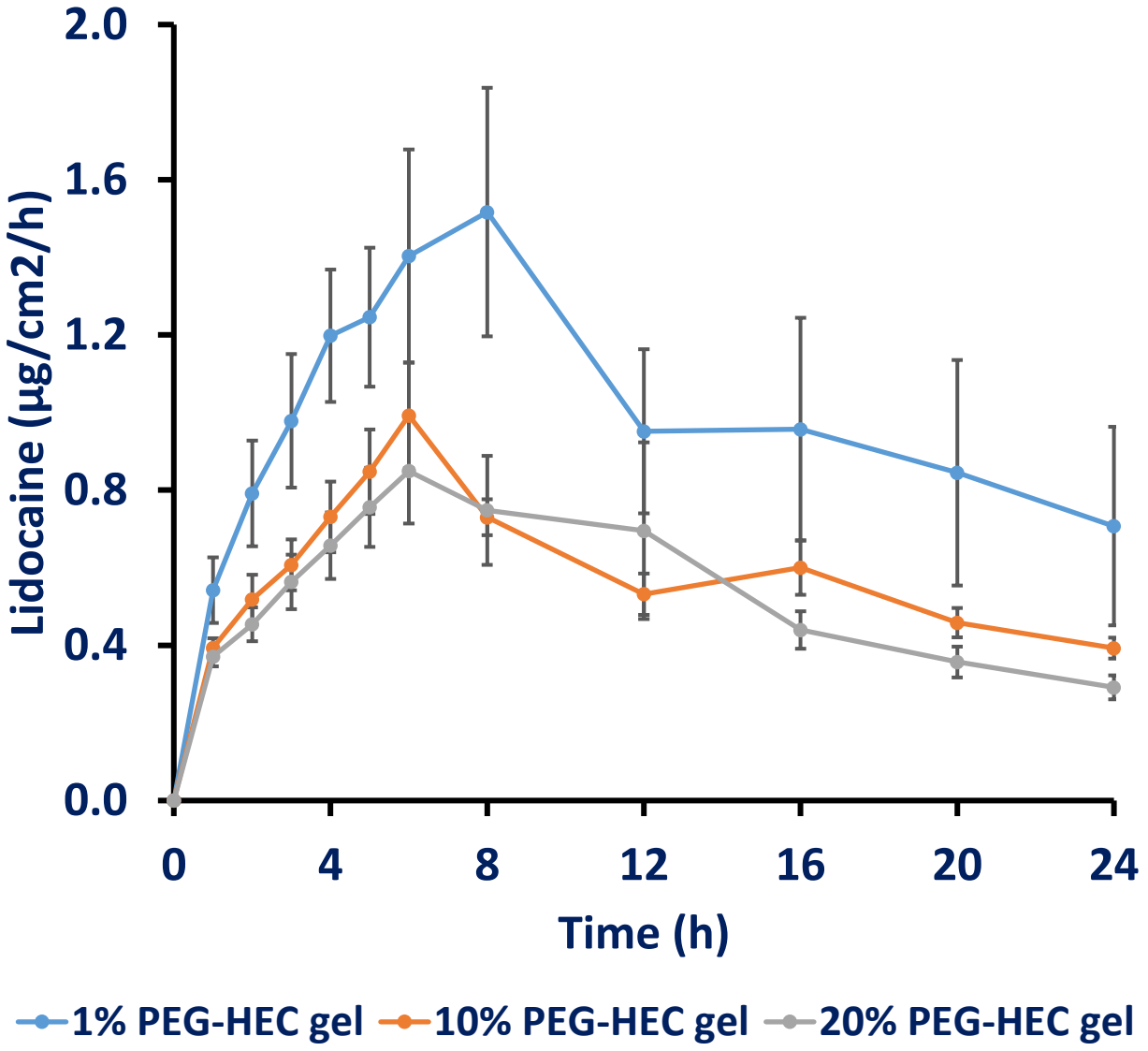
Diclofenac Gel	AUC (µg/cm²)	Jmax (µg/cm²/h)	Tmax (h)
1% PEG 200	10.58 ± 1.31	1.83 ± 0.25	10.67 ± 1.33
10% PEG 200	5.14 ± 0.82	0.79 ± 0.13	10.67 ± 1.33
20% PEG 200	3.97 ± 0.92	0.60 ± 0.17	8.00 ± 0.00

Degree of saturation profile of lidocaine Gels (Semi-finite dose, n=3 ± SEM)





Permeation Flux profile of lidocaine Gels (Semi-finite dose, n=3 ± SEM)



Lidocaine Gel	AUC (µg/cm²)	Jmax (µg/cm²/h)	Tmax (h)
1% PEG 200	23.84 ± 4.35	1.86 ± 0.11	7.33 ± 0.67
10% PEG 200	13.92 ± 0.61	0.99 ± 0.14	6.00 ± 0.00
20% PEG 200	12.87 ± 1.64	0.95 ± 0.17	8.00 ± 2.00

Conclusions

- In case of drugs such as metronidazole, lidocaine and diclofenac sodium, the time course of degree of saturation determines the rate and extent of drug permeation across the skin.

- When formulations are of different compositions (Q1 same and Q2 different), they have comparable Q3 attributes, investigating the degree of saturation-time profile of the products would enable one to predict if the products would be bioequivalent or not.

- Future work will continue exploring the applicability of concepts discussed in this presentation to formulations with other solvents systems such as propylene glycol and PEG-400.

Acknowledgments

TPT LLC, Oxford, MS

- Dr. Howard Maibach (UCSF)
- Dr. Srinath- Chief Scientist
- Dr. Srinivas Ajjarapu
- Dr. Vijaykumar Shankar

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The Office of Generics Drugs (OGD)/Office of Research and Standards (ORS)-USFDA

Dr. Sam Raney

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