SUDA LTD

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ASX Release

SUDA LTD PRESENTS DATA ON NOVEL PENETRATION-ENHANCING TECHNOLOGY

PERTH, AUSTRALIA – 17 November 2016: SUDA LTD (ASX: SUD), a leader in oro-mucosal drug delivery, today announced that Mr. Stephen Carter, Managing Director and CEO, presented data on the Company's novel penetration-enhancing technology at the Annual Symposium of Drug Delivery Systems, being held on 16-19 November 2016 in Nanjing, China.

This scientific conference brings together scientists, academia, healthcare providers, policy makers and investors to provide insights into advances in drug delivery technologies. Mr. Carter chaired a session on "Tackling the Barriers in Different Routes of Drug Delivery."

SUDA recently filed a provisional patent application with IP Australia for its novel mucosal penetration drug delivery technology. Mr. Carter presented data suggesting that the Company's new technology, based on unique combinations of hydrotropes, can significantly enhance the permeation of active drugs through the oro-mucosal membrane into the blood system.

In an *in-vivo* study to evaluate the permeation characteristics of the enhanced formulation of SUDA's proprietary SUD-003 sildenafil oral spray for erectile dysfunction, compared to the original formulation of SUD-003, the new technology resulted in a significant increase in the amount of active sildenafil drug that was absorbed. Further *ex-vivo* studies to test variations of the enhanced SUD-003 formulation suggest that the new technology could provide up to a 10-fold increase in the permeation of sildenafil.

SUDA's CEO, Mr Stephen Carter, commented: "We have achieved significant improvements in the permeation characteristics of sildenafil and many other drugs using our hydrotrope technology. I was pleased to have the opportunity to present our exciting data at such a prestigious scientific event. Based on the technology, our new-generation formulation of SUD-003 could provide meaningful advantages over Viagra® tablets for the treatment of erectile dysfunction."

The presentation follows.

Further information:
STEPHEN CARTER

CHIEF EXECUTIVE OFFICER / MANAGING DIRECTOR
SUDA LTD
Tel: +61 8 6142 5555
sjcarter@sudaltd.com.au

NOTES TO EDITORS:

About SUDA LTD

SUDA LTD (ASX: SUD) is a drug delivery company focused on oro-mucosal administration, headquartered in Perth, Western Australia. The Company is developing low-risk oral sprays using its OroMist® technology to reformulate existing pharmaceuticals. The many potential benefits of administering drugs through the oral mucosa (ie: cheeks, tongue, gums and palate) include ease of use, lower dosage, reduced side effects and faster response time. SUDA's product pipeline includes Zolpimist™, a first-in-class oral spray of zolpidem for insomnia. Zolpimist™ is marketed in the USA and SUDA has rights to the product outside of North America. SUDA's most advanced development-stage product, ArTiMist®, is a novel sublingual malaria treatment for children. In a Phase III trial, ArTiMist® was shown to be superior to intravenous quinine. Other products in development include oral sprays for the treatment of migraine headache, chemotherapy-induced nausea and vomiting, erectile dysfunction and pre-procedural anxiety. For more information, visit www.sudaltd.com.au

SUDA LTD

Drug delivery through the oral mucosa

Novel Formulation Strategies for Overcoming Barriers to Oro-mucosal Drug Delivery

BIT's Annual World Symposium of Drug Delivery Systems
Nanjing, China. 17th November 2016

Stephen Carter
Managing Director
Chief Executive Officer

Company Overview

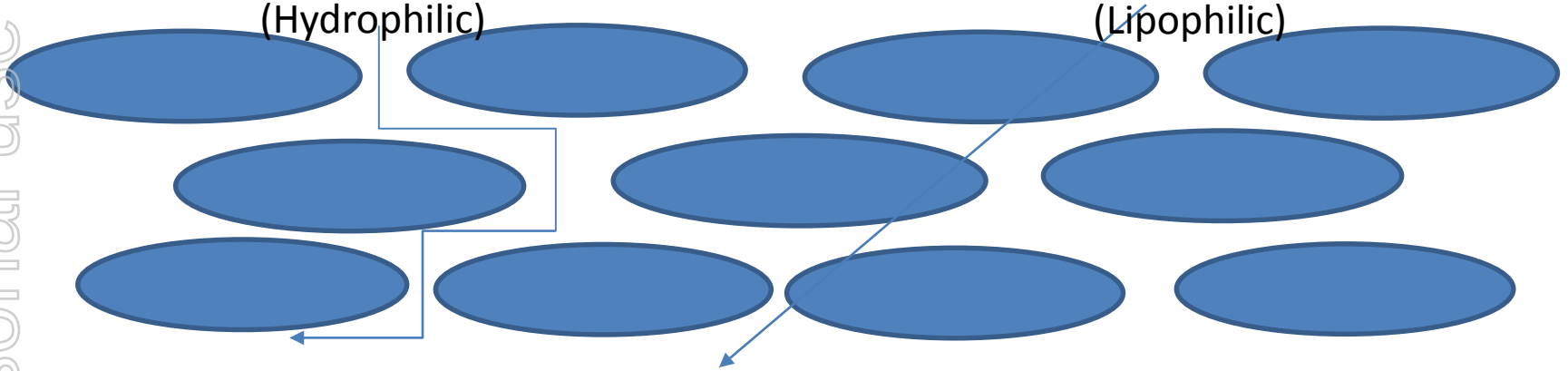
- SUDA is a drug delivery company commercialising low-risk pharmaceuticals
  - Breakthrough sub-lingual spray for treatment of children with severe malaria - completed Phase III trial
  - Multiple oral sprays for large mainstream markets – insomnia, migraine, erectile dysfunction, chemo-induced nausea
- World-leading technology for reformulating drugs into oral sprays with faster onset of action
  - Multiple patent families covering approx. 300 widely-used off-patent drugs
  - Reformulate off-patent pharmaceuticals into high-value patentable oral sprays
  - Demonstrate advantages over standard of care in proof-of-concept trials
  - Out-license in-house programs after PK proof of concept
  - Collaborate on oral spray formulations of APIs of interest to partners
  - Co-development with NCE innovators to enhance TPPs or extend lifecycles with oro-mucosal sprays

Oro-mucosal Tissue Characteristics

- Human buccal and sublingual mucosa is non keratinised.
- Permeability is limited by the lipids and other materials extruded by the membrane coating granules in the cells of the epithelium
- Lipids in non keratinised oro-mucosa consist of amorphous solution of more polar cholesterol esters, cholesterol and glycosphingolids with few lamellae compared to keratinised epithelia

Oro-mucosal Permeation Pathways

- Intercellular (paracellular) (Hydrophilic)
- Intracellular (transcellular) (Lipophilic)

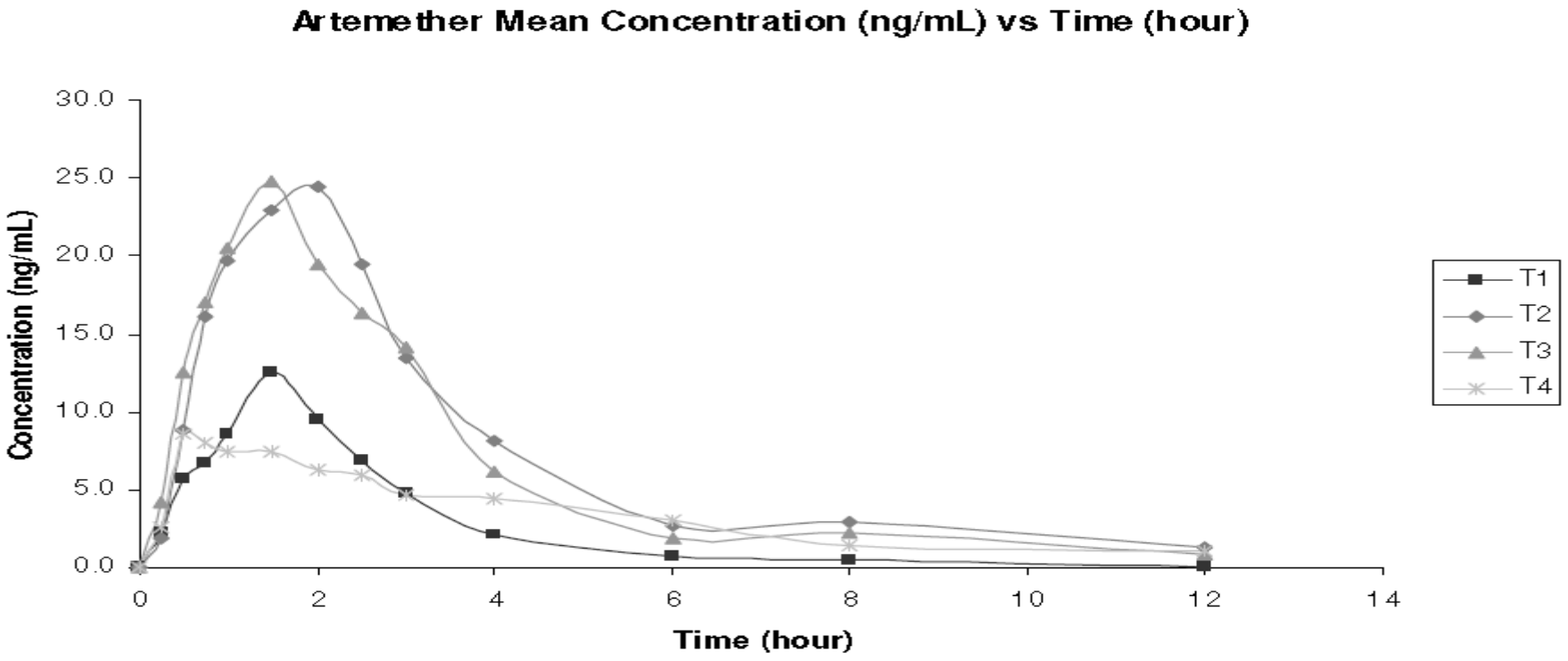


- Experiments have shown that most compounds traverse oro-mucosa via the intercellular pathway
- Sublingual permeation is fastest as thinnest mucosa in this region
- Buccal mucosa thicker mucosa so slower permeation.
- Buccal more suitable where larger surface area required.

Permeability/Penetration Enhancers

- There are a number of methods that have been employed historically to improve the penetration of drugs but I will focus only on chemical enhancers i.e.;
  - Bile Salts,
  - Surfactants.
  - Fatty Acids

ArTiMist™ | ART001 – Mean plasma concentration



Plot of mean plasma Artemether (all measurable peaks) concentration vs. time following a:

T1 - single sublingual administration of 15mg Artemether Sublingual Spray 3mg/actuation

T2 - single sublingual administration of 30mg Artemether Sublingual Spray 3mg/actuation

T3 - single sublingual administration of 30mg Artemether Sublingual Spray 6mg/actuation

T4 - single oral administration of 30mg Artemether tablets (3x10mg tablet)

Novel formulation strategies to enhance buccal permeation

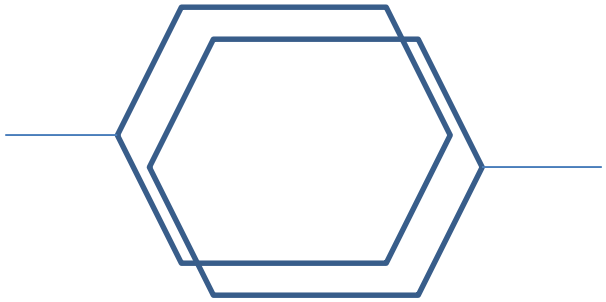
- We needed strategies to improve both speed of transport and total drug permeated.
- Barriers we need to overcome are entry into and permeation through the oromucosa.
- Our solution is a pharmaceutically acceptable group of compounds able to shield the active drug from inhibitory intercellular components and if necessary aid penetration into the mucosa.

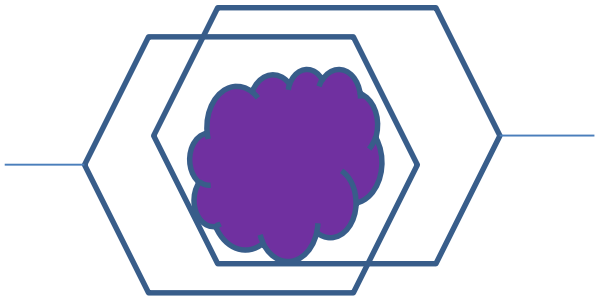
Hydrotropes

- Hydrotropes are broadly defined as a class of compounds which increase the aqueous solubility of sparingly soluble solutes.
- In this discussion hydrotropes are structurally defined as a molecule consisting of a polar and a non-polar end able to aggregate but unable to form micelles

Hydrotrope Stacking Complexation

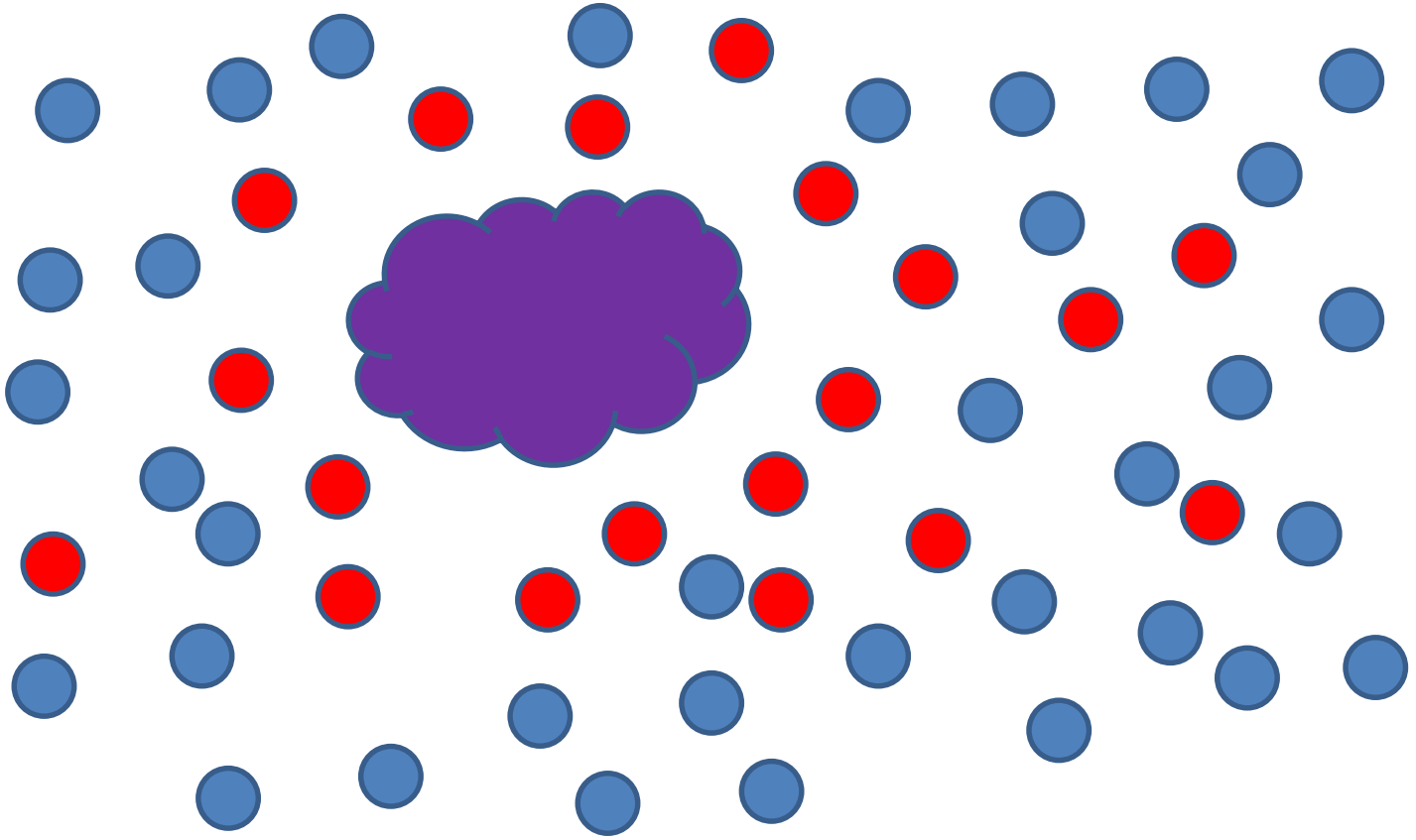
- Hydrotrope stacking theory





Hydrotrope Aggregation

- Hydrotrope aggregation theory



Effects of hydrotropes on permeation

- Careful choice of hydrotrope and hydrotrope mixtures results in active drug hydrotrope complex with an apparent lipophilicity tailored to modify permeability.
- In most cases, this results in increased permeation
- Suda use various methods to evaluate the permeation characteristics;
  - in vitro and ex vivo Franz cell models
  - in vivo rabbit studies.
  - PK studies in Man
- Examples of suitable hydrotropes include, but are not limited to: caffeine, nicotinamide and derivatives, ascorbic acid, citric acid, salicylic acid, benzoic acids, phenols and their corresponding salts, sodium acetate, propyl paraben, sodium alkyl, aryl and alkylaryl sulfonic acids

Hydrotrope/Active classification

- **Hydrotropes** have been classified by binding stability of the various solutes in aqueous solution
- **Class A** hydrotropes contain uncharged aromatic nitrogen and conjugated cyclic amide groups
- **Class B** hydrotropes contain aromatic acids and aldehydes

- **Class A actives** exhibit greatest increases in permeability with Class A hydrotropes
- **Class B** actives exhibit greatest increases in permeability with Class B hydrotropes
- Increases in permeability are not correlated to most stable binding of complexes
- Ionisation and formulation changes can affect classification.

Classification of Actives

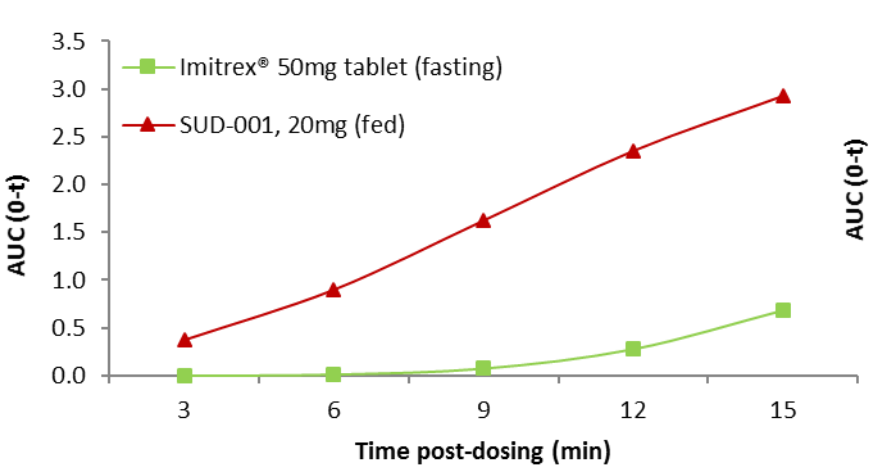
CLASS A Hydrotropes	CLASS B Hydrotropes
Alkylxanthines	Benzoic acid and salts
Caffeine	Salicylates
Theophylline	Ferulic acid
Nicotinamide	Cinnamide
Actives modified permeability with Class A (LogP >1.5)	**Actives modified permeability with Class B (LogP<1.5)**
Ondansetron HCl (LogP 2.4)	Zolpidem tartrate (LogP 1.2)
Sildenafil citrate (LogP 1.9)	Sumatriptan succinate (LogP 0.93)

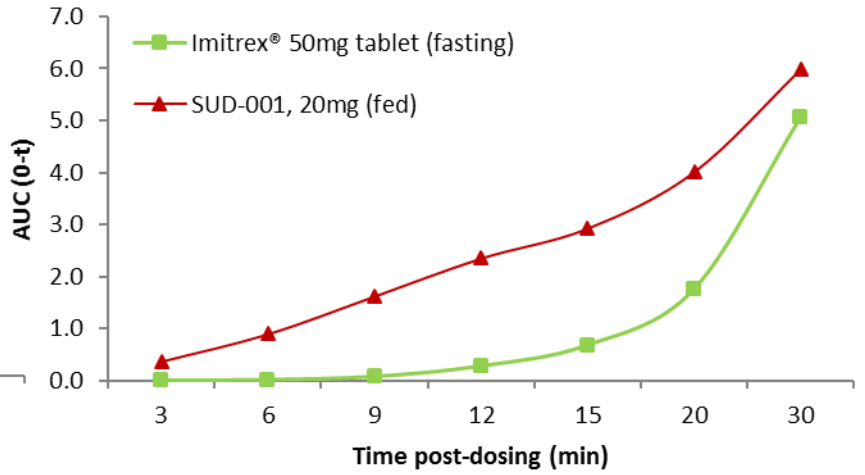
Typical Hydrotrope Concentrations used in formulations

Hydrotrope	Concentration	molwt	mMol/L
Ascorbic acid	0.3%	176	17.0
Benzoic acid	0.5%	122	41.0
Sodium benzoate	0.05% (Sumatriptan only)	144	3.5
Sodium benzoate	0.5%	144	34.7
Caffeine	0.5%	194	25.8
Caffeine	2.5%	194	128.9
Citric acid monohydrate	0.1%	192	5.2
Nicotinamide	0.05%	122	4.1
Nicotinamide	7.5%	122	614.8
Sodium citrate	0.1%	258	3.9
Propyl paraben	0.005%	180	0.3
Sodium acetate	0.05%	82	6.1

Significantly less than used in solubilisation 10-50%
Or in extraction of lipids ~50%

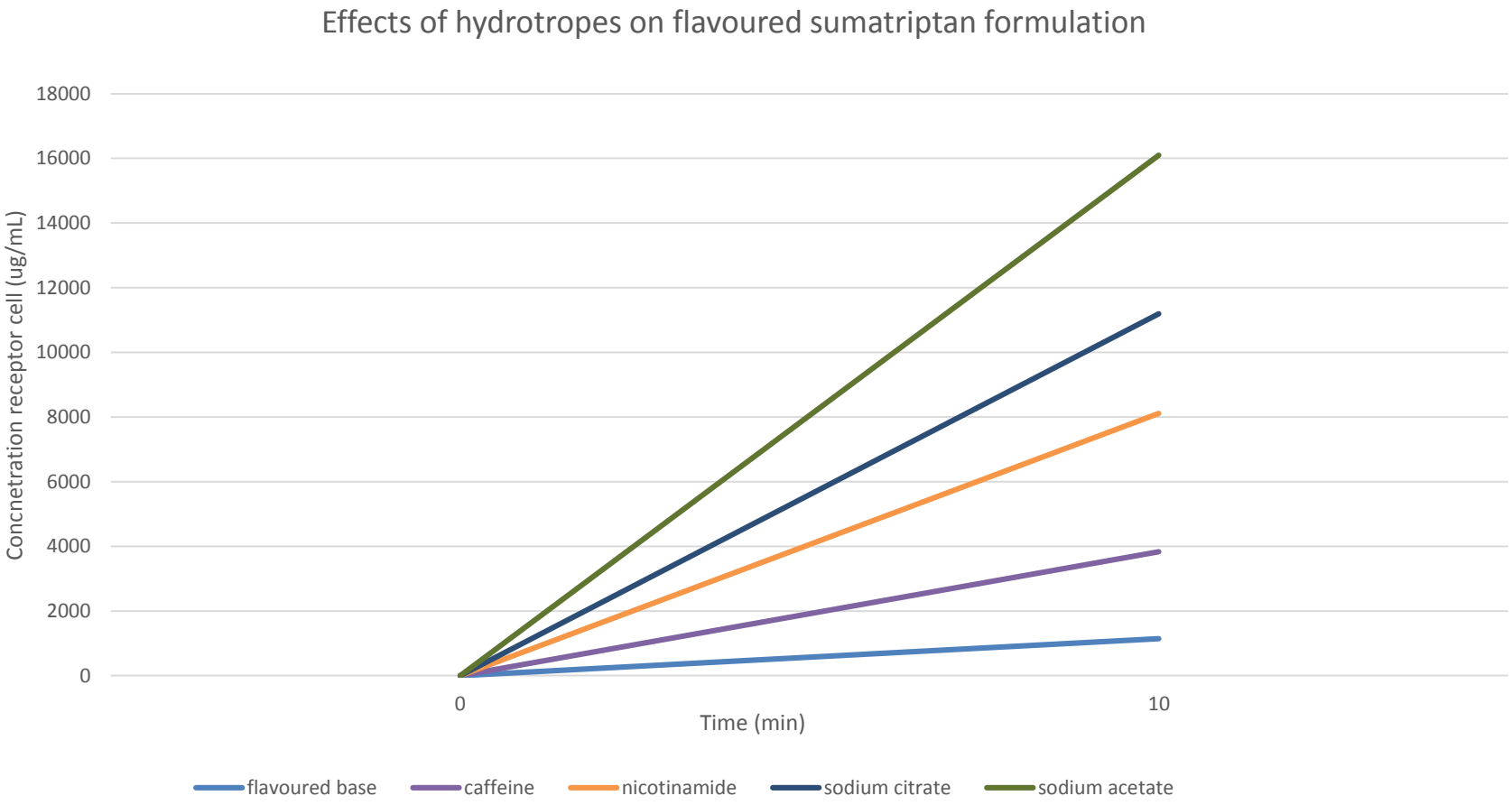
Sumatriptan OS PK results base formulation



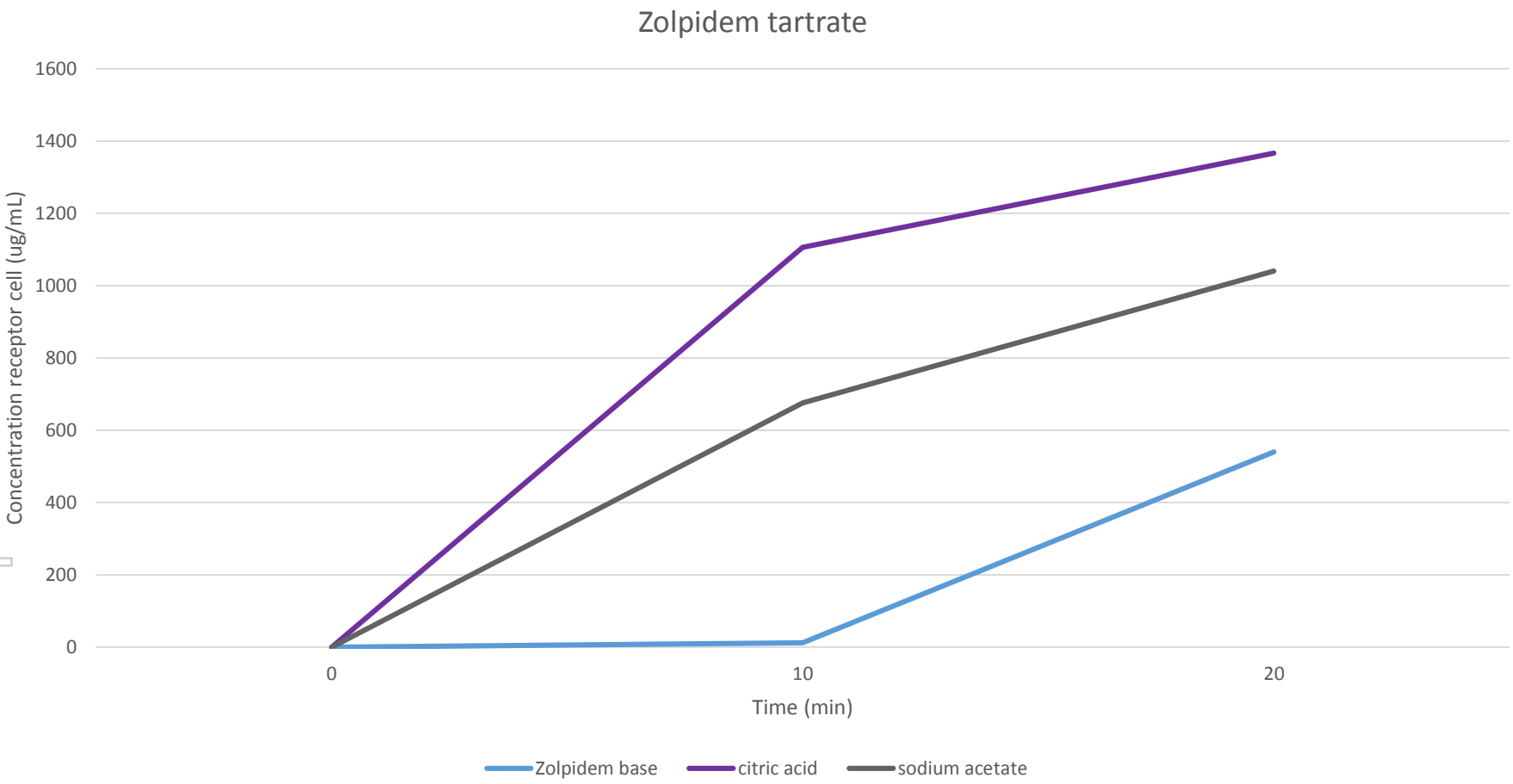


- **Significantly more effective than Imitrex® 50mg, relief paralleling Imitrex® 100mg**
- **Observed 3 fold increase in potency results with 60% less API needed to achieve desired therapeutic effect**
- **Enhanced bioavailability**
- **Rapid onset of action**

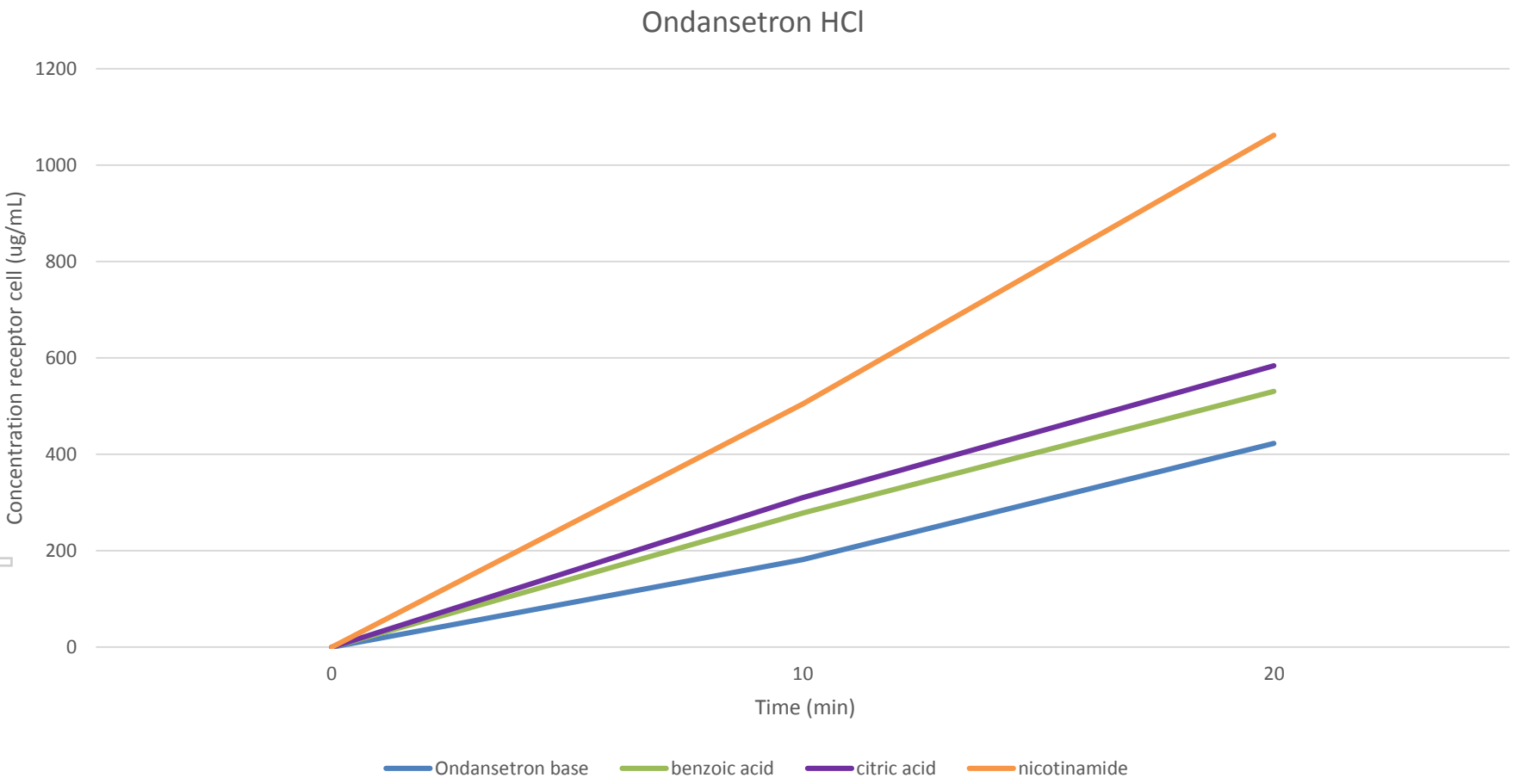
Effects of Hydrotropes on Sumatriptan Flavoured Formulation Permeability in vitro



Effects of Hydrotropes on Zolpidem Tartrate OS



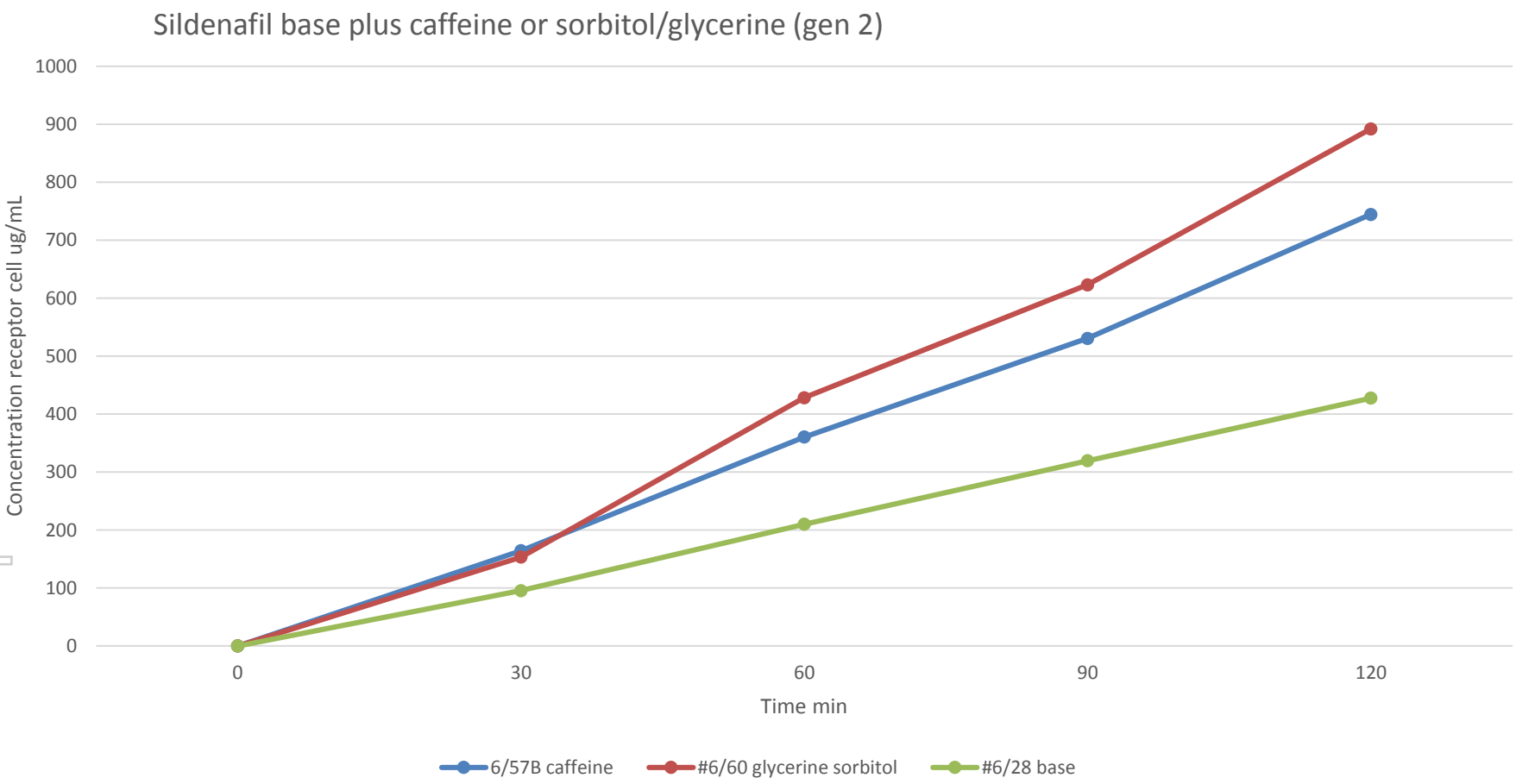
Effect of Hydrotropes on Ondansetron Permeability in vitro



Sildenafil – a case study

- Generation 1 sildenafil formulation had very similar onset of action to tablet form
- Addition of flavour oils and menthol increased permeability in vitro but no significant increase ex vivo porcine buccal membranes
- Generation 2 formulations using glycols, glycerine and oleic acid similar results to above
- Generation 3 formulations using hydrotropes showed increased permeability all models

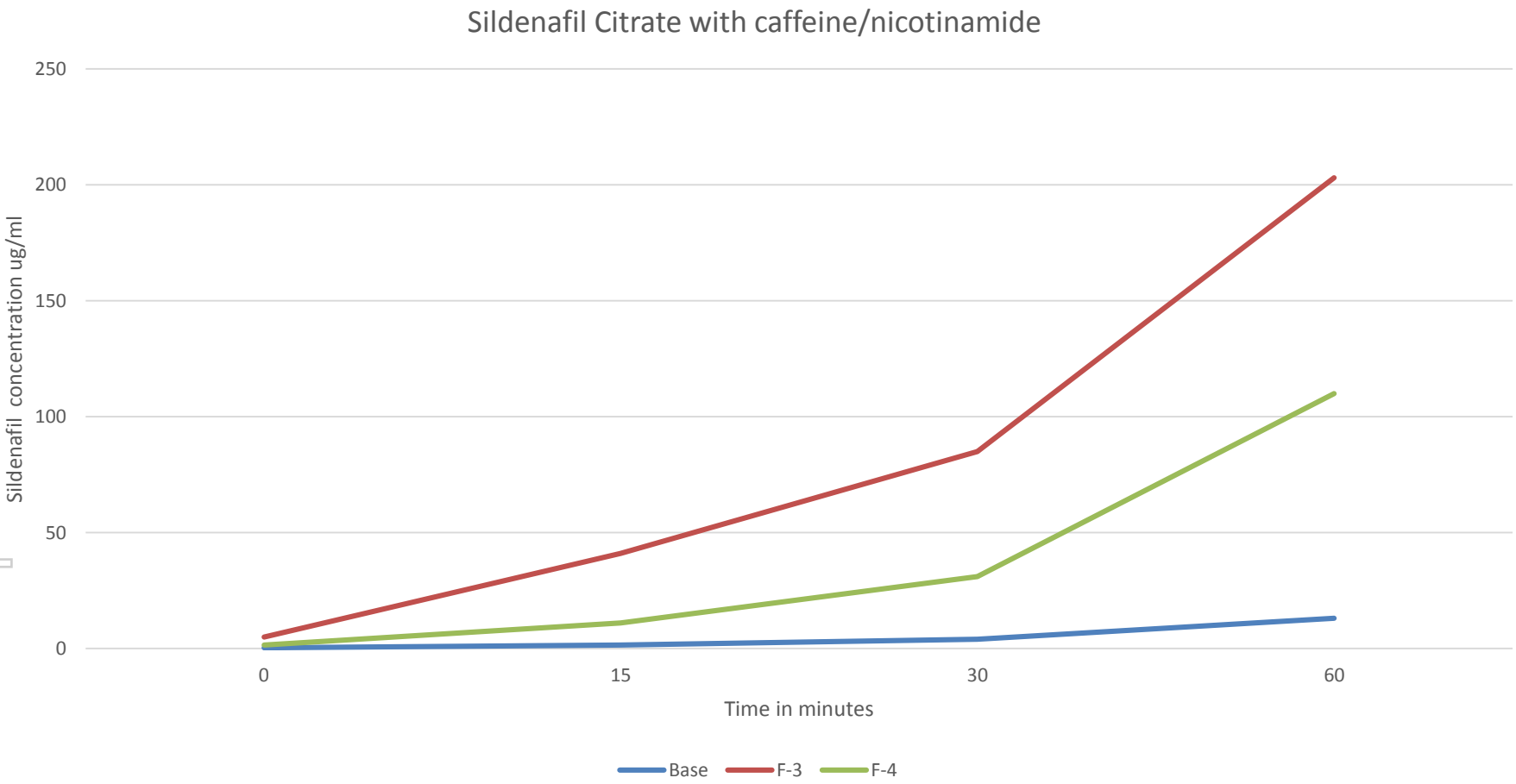
Sildenafil Formulation Development Artificial Membrane



Mixed hydrotropes for maximum permeability modification

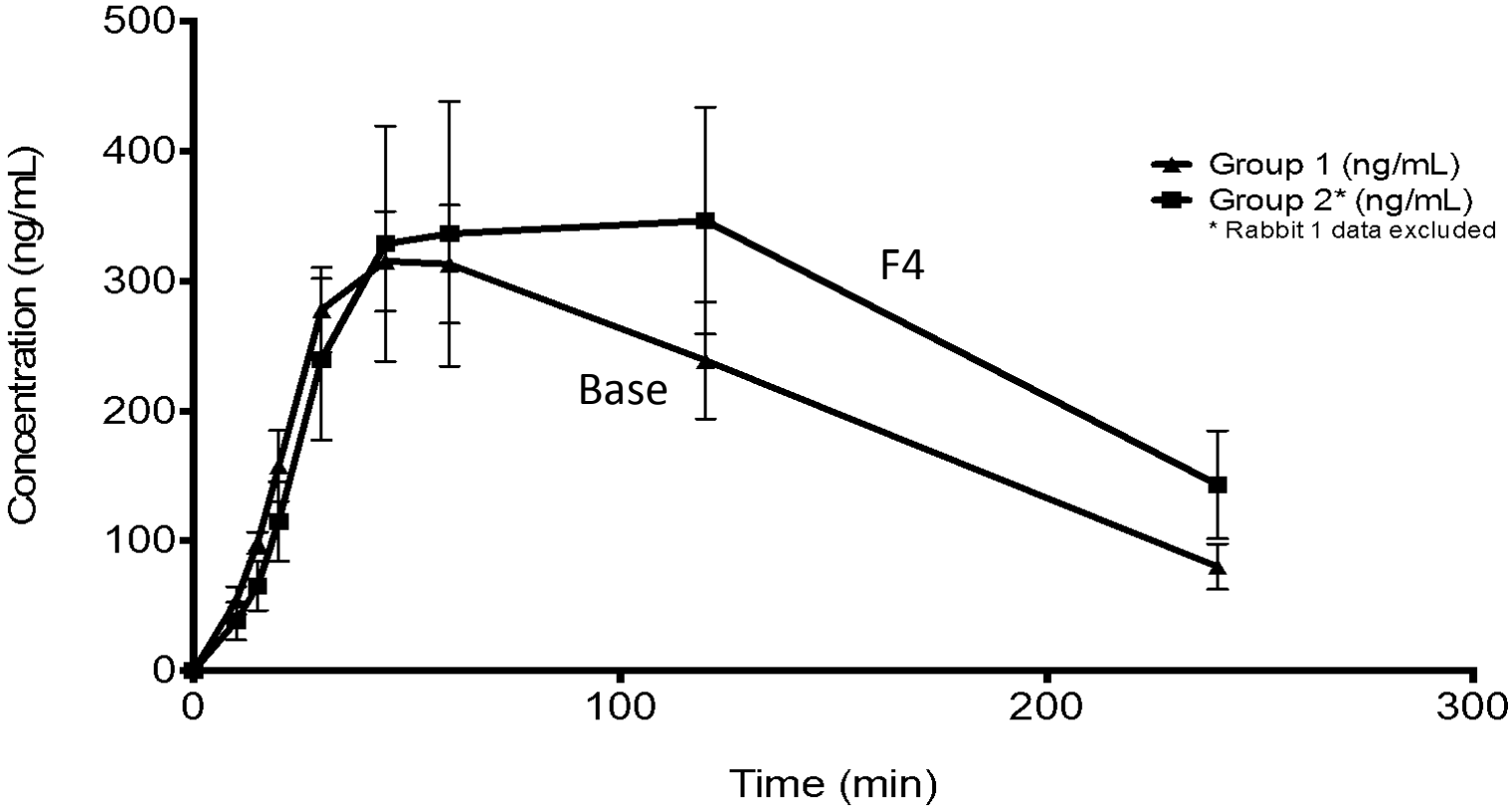
- Hydrotropes are known to act synergistically in solubilisation
- This property has been utilised in optimisation of permeability modifications for formulations.
- Sildenafil achieves maximum permeability with paired hydrotropes caffeine and nicotinamide

Effects of Paired Hydrotropes in Sildenafil Permeability ex vivo (porcine)

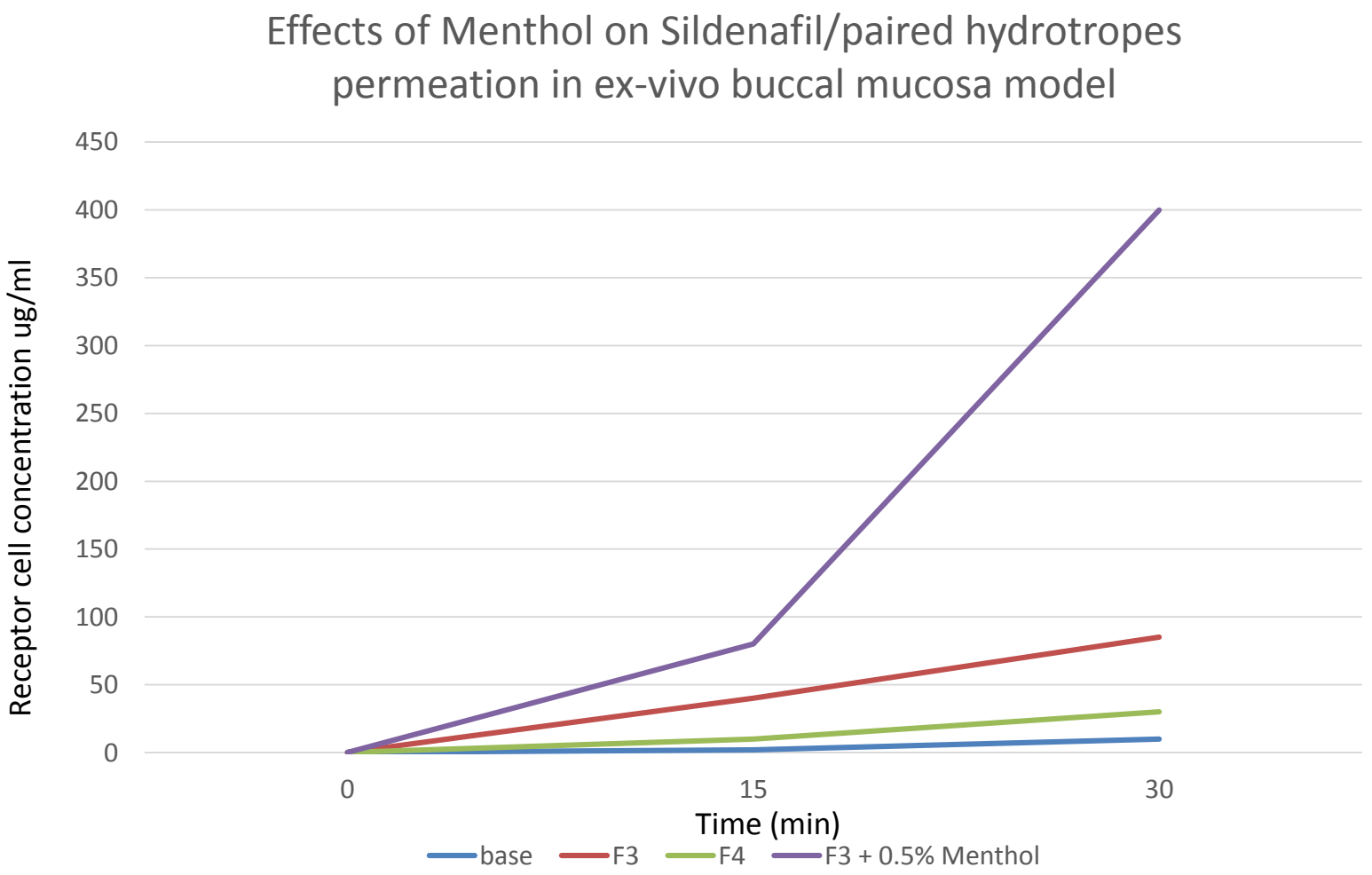


Effects of Paired Hydrotropes on Sildenafil Permeability in vivo (rabbits)

Group1 control Group 2 paired hydrotropes



Effects of addition of menthol flavour to sildenafil paired hydrotrope formulation ex vivo



Summary

- Passage through the buccal mucosa affected by;
  - Lipophilic nature of drug
  - Intercellular pathway inter-dispersed with lipids, lipid lamella and proteins
- At low concs hydrotrope activity alters apparent lipophilicity of compound to modify;
  - Entry into buccal mucosa
  - Passage through the intracellular spaces
- Resulting in greater permeability that may result in;
  - Faster onset of action
  - Less drug required to get same PK result
  - Better side effect/toxicity profile.

Level 1, Unit 12,
55 Howe Street
Osborne Park,
Western Australia 6017
PO Box 1719
Osborne Park BC, WA 6916

(T) +61 8 6142 5555
(F) +61 8 9443 8858
(E) suda@sudaltd.com.au