

Maisine[®]: oily vehicle for lipid-based formulation

Literature review August 2016



In this literature review you will find **a selection of the most relevant articles about Maisine[®] (Glyceryl monolinoleate) as an oily vehicle for Lipid-Based Formulations (LBF)**. Full text articles cannot be given to customers due to copyright restrictions. However, complete references of the publications are included to enable customers to order articles themselves. For your personal use, you can read the article directly in your browser using the "reference manager" link in intranet/extranet.

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Articles with drug solubility data in Maisine

Garg, B., Katare, O. P., Beg, S., Lohan, S., & Singh, B. (2016). Systematic development of solid self-nanoemulsifying oily formulations (S-SNEOFs) for enhancing the oral bioavailability and intestinal lymphatic uptake of **lopinavir**. *Colloids and Surfaces B: Biointerfaces*, 141, 611-622.

Kamboj, S., & Rana, V. (2016). Quality-by-design based development of a self-microemulsifying drug delivery system to reduce the effect of food on **Nelfinavir mesylate**. *International journal of pharmaceutics*, 501(1), 311-325.

Alskär, L. C., Porter, C. J., & Bergström, C. A. (2015). Tools for Early Prediction of Drug Loading in Lipid-Based Formulations. *Molecular pharmaceutics*.

In this article the authors compare solubility data from 35 APIs in 4 different glycerides, including Maisine, and 4 different surfactants. The purpose is to establish a tool to predict drug loading in a LBF as a function of solubility data in individual excipients and drug intrinsic properties.

Kulkarni, N. S., Ranpise, N. S., & Mohan, G. (2015). Development and Evaluation of Solid Self Nano-Emulsifying Formulation of **Rosuvastatin Calcium** for Improved Bioavailability. *Tropical Journal of Pharmaceutical Research*, 14(4), 575-582.

Singh, G., & Pai, R. S. (2014). Optimized self-nanoemulsifying drug delivery system of **atazanavir** with enhanced oral bioavailability: *in vitro/in vivo* characterization. *Expert opinion on drug delivery*, 11(7), 1023-1032.

Devraj, R., Williams, H. D., Warren, D. B., Mohsin, K., Porter, C. J., & Pouton, C. W. (2013). *In vitro* assessment of drug-free and **fenofibrate**-containing lipid formulations using dispersion and digestion testing gives detailed insights into the likely fate of formulations in the intestine. *European Journal of Pharmaceutical Sciences*, 49(4), 748-760.

Bandyopadhyay, S., Katare, O. P., & Singh, B. (2012). Optimized self nano-emulsifying systems of **ezetimibe** with enhanced bioavailability potential using long chain and medium chain triglycerides. *Colloids and Surfaces B: Biointerfaces*, 100, 50-61.

Rahman, M. A., Iqbal, Z., & Hussain, A. (2012). Formulation optimization and *in vitro* characterization of **sertraline** loaded self-nanoemulsifying drug delivery system for oral administration. *Journal of Pharmaceutical investigation*, 42(4), 191-202.

Sacchetti, M., & Nejati, E. (2012). Prediction of drug solubility in lipid mixtures from the individual ingredients. *AAPS PharmSciTech*, 13(4), 1103-1109.

In this article the authors compare solubility data from 4 APIs in 18 different excipients, including Maisine, currently used in LBF formulations. The purpose is to establish a tool to predict drug solubility in lipid mixtures as a function of solubility data in individual excipients.

Thomas, N., Müllertz, A., Graf, A., & Rades, T. (2012). Influence of lipid composition and drug load on the *In vitro* performance of self-nanoemulsifying drug delivery systems. *Journal of pharmaceutical sciences*, 101(5), 1721-1731.

Aburahma, M. H., El-Laithy, H. M., & Hamza, Y. E. S. (2010). Oral bioavailability enhancement of vinpocetine using self-microemulsifying drug delivery system containing long chain triglycerides: Preparation and *in vitro/in vivo* evaluation. *Clinical Research and Regulatory Affairs*, 27(4), 97-107.

Articles with oral bioavailability data of Maisine-containing LBF

Garg, B., Katare, O. P., Beg, S., Lohan, S., & Singh, B. (2016). Systematic development of solid self-nanoemulsifying oily formulations (S-SNEOFs) for enhancing the oral bioavailability and intestinal lymphatic uptake of **lopinavir**. *Colloids and Surfaces B: Biointerfaces*, 141, 611-622.

In this study the purpose is to develop a formulation targeting the lymphatic system for HIV treatment with lopinavir. The *in vivo* study is carried out on rats, treated or not with cycloheximide. The optimized LBF formulation developed contains Maisine, Tween 80 and Transcutol. Both a liquid and solid LBF are compared and pharmacokinetic profiles are given.

Kulkarni, N. S., Ranpise, N. S., & Mohan, G. (2015). Development and Evaluation of Solid Self Nano-Emulsifying Formulation of **Rosuvastatin Calcium** for Improved Bioavailability. *Tropical Journal of Pharmaceutical Research*, 14(4), 575-582.

In this study, several LBF (liquid and solid) are compared both *in vitro* and *in vivo* on rats. An optimized formulation is given, which exhibits spontaneous emulsification properties and superior *in vivo* properties compared to drug alone.

Singh, G., & Pai, R. S. (2014). Optimized self-nanoemulsifying drug delivery system of **atazanavir** with enhanced oral bioavailability: *in vitro/in vivo* characterization. Expert opinion on drug delivery, 11(7), 1023-1032.

This article describes the development and characterization of a LBF, coupled with *in vitro* and *in vivo* tests. The optimized formulation exhibits better oral bioavailability, possibly attributed to increase lymphatic transport.

Bandyopadhyay, S., Katare, O. P., & Singh, B. (2012). Optimized self nano-emulsifying systems of **ezetimibe** with enhanced bioavailability potential using long chain and medium chain triglycerides. *Colloids and Surfaces B: Biointerfaces*, 100, 50-61.

In this study an optimized LC LBF and a MC LBF are compared for oral bioavailability, versus pure drug, market reference and beta cyclodextrin complex. Long chain triglyceride-based formulation gives the best results *in vivo* in rats.

Chen, Z.-Q., Liu, Y., Zhao, J.-H., Wang, L., & Feng, N.-P. (2012). Improved oral bioavailability of poorly water-soluble indirubin by a supersaturatable self-microemulsifying drug delivery system. *International Journal of Nanomedicine*, 7, 1115-1125.

SMEDDS are formulated to improve oral bioavailability of indirubin, using Maisine, Cremophor and Transcutol. The supersaturated SMEDDS is shown to have higher relative bioavailability (129%) compared to standard SMEDDS.

Aburahma, M. H., El-Laithy, H. M., & Hamza, Y. E. S. (2010). Oral bioavailability enhancement of vinpocetine using self-microemulsifying drug delivery system containing long chain triglycerides: Preparation and *in vitro/in vivo* evaluation. *Clinical Research and Regulatory Affairs*, 27(4), 97-107.

The authors describe the preparation, characterization and evaluation of LBFs of vinpocetine. *In vivo* study in rats compares optimized formulation to market reference tablets.

Singla, N., Gupta, G. D., Kohli, K., & Jain, S. (2009). Oral bioavailability of simvastatin novel formulation in albino rats. *J Pharm Sci Techol*, 1, 84-87.

In this study an optimized LBF is evaluated *in vivo* in rats, in comparison to the market reference (tablet). The LBF formulation strongly increases the oral bioavailability of simvastatin.

Cuiné, J. F., Charman, W. N., Pouton, C. W., Edwards, G. A., & Porter, C. J. (2007). Increasing the proportional content of surfactant (Cremophor EL) relative to lipid in self-emulsifying lipid-based formulations of danazol reduces oral bioavailability in beagle dogs. *Pharmaceutical research*, 24(4), 748-757.

Formulations with varying proportions of oils (soybean oil:Maisine), surfactant (Cremophor) and ethanol are assessed for drug solubilization and bioavailability in rats. The higher the surfactant concentration (and hence the lower the lipid concentration) the lower the bioavailability.

Caliph, S. M., Charman, W. N., & Porter, C. J. (2000). Effect of short-, medium-, and long-chain fatty acid-based vehicles on the absolute oral bioavailability and intestinal lymphatic transport of halofantrine and assessment of mass balance in lymph-cannulated and non-cannulated rats. *Journal of pharmaceutical sciences*, 89(8), 1073-1084.

In this study the effect of chain length of lipids on halofantrine lymphatic transport is clearly demonstrated *in vivo* in rats: the longer the lipid chain, the higher the halofantrine content in lymph. A strong correlation is observed between triglyceride transport into the lymph and halofantrine transport into the lymph.

Articles on lymphatic transport

Garg, B., Katare, O. P., Beg, S., Lohan, S., & Singh, B. (2016). Systematic development of solid self-nanoemulsifying oily formulations (S-SNEOFs) for enhancing the oral bioavailability and intestinal lymphatic uptake of **lopinavir**. *Colloids and Surfaces B: Biointerfaces*, 141, 611-622.

Trevaskis, N. L., Kaminskis, L. M., & Porter, C. J. (2015). From sewer to saviour targeting the lymphatic system to promote drug exposure and activity. *Nature Reviews Drug Discovery*.

In this excellent review article the authors give an update on the lymphatic system: its constitution, how drug can enter the lymphatic vessels through parenteral, oral and mucosal route of administration, what therapeutic advantages the lymphatic delivery brings in cancer treatment, immunomodulation, parenteral and mucosal vaccination. On top of that, the review is punctuated with clear illustrations to help understand how the lymphatic system works.

El-Laithy, H. M., Basalious, E. B., El-Hoseiny, B. M., & Adel, M. M. (2015). Novel self-nanoemulsifying self-nanosuspension (SNESNS) for enhancing oral bioavailability of diacerein: Simultaneous portal blood absorption and lymphatic delivery. *International journal of pharmaceuticals*, 490(1), 146-154.

In this study a LBF is developed specifically to benefit from the lymphatic transport of the drug to increase total oral bioavailability. *In vivo* studies are carried out in cycloheximide treated versus non treated rats.

Trevaskis, N. L., McEvoy, C. L., McIntosh, M. P., Edwards, G. A., Shanker, R. M., Charman, W. N., & Porter, C. J. (2010). The role of the intestinal lymphatics in the absorption of two highly lipophilic cholesterol ester transfer protein inhibitors (CP524, 515 and CP532, 623). *Pharmaceutical research*, 27(5), 878-893.

In this study a LBF is developed specifically to benefit from the lymphatic transport of the drug to increase global oral bioavailability. *In vivo* studies are carried out on dogs, lymph cannulated or not.

Trevaskis, N. L., Shackleford, D. M., Charman, W. N., Edwards, G. A., Gardin, A., Appel-Dingemanse, S. & Porter, C. J. (2009). Intestinal lymphatic transport enhances the post-prandial oral bioavailability of a novel cannabinoid receptor agonist via avoidance of first-pass metabolism. *Pharmaceutical research*, 26(6), 1486-1495.

In this study a LBF is developed specifically to target the lymphatic transport of the drug to increase overall oral bioavailability. *In vivo* studies are carried out in lymph cannulated versus non cannulated dogs.

Trevaskis, N. L., Charman, W. N., & Porter, C. J. (2008). Lipid-based delivery systems and intestinal lymphatic drug transport: a mechanistic update. *Advanced drug delivery reviews*, 60(6), 702-716.

In this review the authors provide an overview of the current knowledge on intestinal lymphatic drug transport and describe the *in vivo* and *in vitro* models. A detailed description of how lipids are digested and absorbed is given.

Khoo, S. M., Shackleford, D. M., Porter, C. J., Edwards, G. A., & Charman, W. N. (2003). Intestinal lymphatic transport of halofantrine occurs after oral administration of a unit-dose lipid-based formulation to fasted dogs. *Pharmaceutical research*, 20(9), 1460-1465.

In this study the lymphatic transport of the drug is evaluated *in vivo* in lymph cannulated versus non cannulated dogs. This study clearly sets out that long chain glycerides favor lymphatic transport compared to medium chain glycerides.

Reddy, L. H. V., & Murthy, R. S. R. (2002). Lymphatic transport of orally administered drugs. *Indian journal of experimental biology*, 40(10), 1097-1109.

Caliph, S. M., Charman, W. N., & Porter, C. J. (2000). Effect of short-, medium-, and long-chain fatty acid-based vehicles on the absolute oral bioavailability and intestinal lymphatic transport of halofantrine and assessment of mass balance in lymph-cannulated and non-cannulated rats. *Journal of pharmaceutical sciences*, 89(8), 1073-1084.

Articles on the effect of lipid chain length

Devraj, R., Williams, H. D., Warren, D. B., Mohsin, K., Porter, C. J., & Pouton, C. W. (2013). *In vitro* assessment of drug-free and fenofibrate-containing lipid formulations using dispersion and digestion testing gives detailed insights into the likely fate of formulations in the intestine. *European Journal of Pharmaceutical Sciences*, 49(4), 748-760.

The authors compare long chain lipids (soybean oil, Maisine) vs medium chain lipids (Miglyol, Inwitor) in type II or type IIIA LBF formulations. Although fenofibrate solubility is higher in MC LBF, the oral bioavailability is higher for LC LBF, as observed with *in vitro* digestion test.

Bandyopadhyay, S., Katare, O. P., & Singh, B. (2012). Optimized self nano-emulsifying systems of ezetimibe with enhanced bioavailability potential using long chain and medium chain triglycerides. *Colloids and Surfaces B: Biointerfaces*, 100, 50-61.

Thomas, N., Müllertz, A., Graf, A., & Rades, T. (2012). Influence of lipid composition and drug load on the *In vitro* performance of self-nanoemulsifying drug delivery systems. *Journal of pharmaceutical sciences*, 101(5), 1721-1731.

In this study SNEDD formulations are compared with respect to the lipid chain length (soybean oil:Maisine vs Captex:Capmul) and surfactant nature (Cremophor EL vs Cremophor RH 40).

Porter, C. J., Pouton, C. W., Cuine, J. F., & Charman, W. N. (2008). Enhancing intestinal drug solubilisation using lipid-based delivery systems. *Advanced Drug Delivery Reviews*, 60(6), 673-691.

In this article the authors describe the processing of lipids in the intestinal lumen and how to assess LBF using an *in vitro* lipolysis test.

Kossena, G. A., Charman, W. N., Boyd, B. J., & Porter, C. J. (2005). Influence of the intermediate digestion phases of common formulation lipids on the absorption of a poorly water-soluble drug. *Journal of pharmaceutical sciences*, 94(3), 481-492.

Different combinations of C8, C12 or C18:1 lipids were formulated to provide examples of liquid, lamellar and cubic liquid crystalline phases. The effect of each phase on cinnarizine solubilization and absorption in rats was assessed.

Porter, C. J. H., Kaukonen, A. M., Boyd, B. J., Edwards, G. A., and Charman, W. N. (2004). Susceptibility to Lipase-Mediated Digestion Reduces the Oral Bioavailability of **Danazol** After Administration as a Medium-Chain Lipid-Based Microemulsion Formulation. *Pharmaceutical Research*, 21[8], 1405-1412.

In this study three formulations are compared: LCT solution, LC SMEDDS and MC SMEDDS after administration to dogs. The LC formulations significantly enhance the oral bioavailability of danazol in dogs. *In vitro* results confirm that with MC formulation a strong precipitation of the drug occurs.

Caliph, S. M., Charman, W. N., & Porter, C. J. (2000). Effect of short-, medium-, and long-chain fatty acid-based vehicles on the absolute oral bioavailability and intestinal lymphatic transport of halofantrine and assessment of mass balance in lymph-cannulated and non-cannulated rats. *Journal of pharmaceutical sciences*, 89(8), 1073-1084.

Articles on the digestion of lipids

Kamboj, S., & Rana, V. (2016). Quality-by-design based development of a self-microemulsifying drug delivery system to reduce the effect of food on **Nelfinavir mesylate**. *International journal of pharmaceutics*, 501(1), 311-325.

In this study a LBF containing Maisine, Transcutol and Tween 80 is designed to enhance drug solubility and oral bioavailability to eliminate the food effect.

Holm, R., Müllertz, A., & Mu, H. (2013). Bile salts and their importance for drug absorption. *International journal of pharmaceutics*, 453(1), 44-55.

In this review article a full panorama on bile salts composition in different species is given. Their effect on drug delivery is described for solid formulations, cyclodextrin formulations and lipid-based formulations.

Williams, H. D., Trevaskis, N. L., Yeap, Y. Y., Anby, M. U., Pouton, C. W., & Porter, C. J. (2013). Lipid-based formulations and drug supersaturation: Harnessing the unique benefits of the lipid digestion/absorption pathway. *Pharmaceutical research*, 30(12), 2976-2992.

This article explains the mechanisms by which LBF enhance the absorption of drugs by stimulating solubilization and supersaturation.

Kossena, G. A., Charman, W. N., Wilson, C. G., O'Mahony, B., Lindsay, B., Hempenstall, J. M., Davison, C. L., Crowley, P. J., and Porter, C. J. H. (2007). Low dose lipid formulations: effects on gastric emptying and biliary secretion. *Pharmaceutical Research*, 24[11], 2084-2096.

This study shows that low quantity of lipids is sufficient to stimulate gall bladder contraction and to increase the quantity of bile salts, and in turn to enhance the absorption of drugs from LBF.

Kaukonen, A. M., Boyd, B. J., Porter, C. J., & Charman, W. N. (2004). Drug solubilization behavior during *in vitro* digestion of simple triglyceride lipid solution formulations. *Pharmaceutical research*, 21(2), 245-253.

Using five model drugs, the authors describe their solubilization in different triglycerides formulations.

Charman, W. N., Rogge, M. C., Boddy, A. W., and Berger, B. M. (1993). Effect of food and a monoglyceride emulsion formulation on danazol bioavailability. *The Journal of Clinical Pharmacology*, 33[4], 381-386.

A higher bioavailability of danazol is obtained with the LBF compared to market reference capsules without food effect.

Articles with data on marketed LBF

Gibaud, S., & Attivi, D. (2012). Microemulsions for oral administration and their therapeutic applications. *Expert opinion on drug delivery*, 9(8), 937-951.

In this review, the authors describe how to formulate and characterize microemulsions. Commercial and potential applications are described.

Alexander, A. (2012). A review on novel therapeutic strategies for the enhancement of solubility for hydrophobic drugs through lipid and surfactant based self micro emulsifying drug delivery system: a novel approach. *Am. J. Drug Disc. Develop*, 2(4), 143-183.

This review article describes SMEDDS, their formulation, characterization and use. Market references of SMEDDS are given and scientific and patent literature is reviewed.

Müllertz, A., Ogbonna, A., Ren, S., & Rades, T. (2010). New perspectives on lipid and surfactant based drug delivery systems for oral delivery of poorly soluble drugs. *Journal of pharmacy and pharmacology*, 62(11), 1622-1636.

This review article explains how to develop LBF, select the lipid and surfactant and use the *in vitro* lipolysis tests to evaluate the LBF. The LBF classification system developed by the LFCS is applied on market references and formulations of major scientific references.

Chakraborty, S., Shukla, D., Mishra, B., & Singh, S. (2009). Lipid—an emerging platform for oral delivery of drugs with poor bioavailability. *European Journal of Pharmaceutics and Biopharmaceutics*, 73(1), 1-15.

In this review article, the role of lipids in bioavailability enhancement is described. The design of LBF is detailed, as well as *in vitro* and *in vivo* methods to characterize them. Examples of marketed products are given.

Strickley, R. G. (2004). Solubilizing excipients in oral and injectable formulations. *Pharmaceutical Research*, 21[2], 201-230.

The author reviews the main techniques used to solubilize drugs for oral and parenteral administration through analysis of many commercial specialties.

General articles on LBF

Chakraborty, S., Shukla, D., Mishra, B., & Singh, S. (2009). Lipid—an emerging platform for oral delivery of drugs with poor bioavailability. *European Journal of Pharmaceutics and Biopharmaceutics*, 73(1), 1-15.

Jannin, V., Musakhanian, J., & Marchaud, D. (2008). Approaches for the development of solid and semi-solid lipid-based formulations. *Advanced drug delivery reviews*, 60(6), 734-746.

This article summarizes the lipid excipients available for LBF and explains the rationale for excipient selection. The techniques to develop solid LBF are described.

Pouton, C. W., & Porter, C. J. (2008). Formulation of lipid-based delivery systems for oral administration: materials, methods and strategies. *Advanced Drug Delivery Reviews*, 60(6), 625-637.

In this review lipid excipients are described as well as formulation tools. Tips are given for each LFCS type of formulation.

Porter, C. J., Pouton, C. W., Cuine, J. F., & Charman, W. N. (2008). Enhancing intestinal drug solubilisation using lipid-based delivery systems. *Advanced Drug Delivery Reviews*, 60(6), 673-691.

In this article the authors describe the processing of lipids in the intestinal lumen and how to assess LBF using an *in vitro* lipolysis test.