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OPTIMISATION OF CURCUMIN MICROEMULSIONS USING PALM OIL

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ABSTRACT

Curcumin is a natural hydrophobic polyphenol derived from the curcuminoids of Curcuma longa. Curcumin is commonly known as turmeric and it gains the interest of scientific and clinical researchers as it exhibits great pharmacological benefits such as anti-cancer, anti-inflammatory and anti-oxidant properties. Nevertheless, curcumin is still not an approved drug in clinical settings due to its poor aqueous solubility and low oral bioavailability. Therefore, a self-microemulsifying drug delivery system (SMEDDS) was used as an approach to enhance the solubility and bioavailability of curcumin. The microemulsion was devised in a pre-formulation phase using a surfactant (Tween 80), a co-surfactant (polyethylene glycol, PEG 400), a lipid phase (palm oil) and an aqueous phase (water). A ternary phase diagram was used to identify the self-microemulsifying region in a formulation. Five of these formulations (F1, F2, F4, F7 and F10) were found to be stable with no phase separation observed upon overnight storage. All of the five formulations (except F4) possessed a high percentage of transmittance (86%–100%), which signified the formation of a stable microemulsion when they were diluted in a 1:100 ratio by water. Curcumin microemulsions were formulated by loading curcumin into F1, F2, F7 and F10. Only F1 and F2 curcumin microemulsions exhibit a clear appearance, however, F7 and F10 form a turbid solution, which indicates the formation of the emulsion. The results indicated that F1 and F2 which contain a high surfactant/co-surfactant-to-oil ratio of 9:1 is optimum to formulate the curcumin microemulsions.

Keywords: Curcumin, Microemulsion, Self-microemulsifying drug delivery system

INTRODUCTION

Curcumin (Figure 1) is a naturally occurring constituent of yellow pigment which has considerable scientific and clinical interest to attract researchers due to its diverse phytochemical properties (Priyadarsini 2014). Curcumin is extensively used in Asian medicines, as well as preservatives, colouring and flavouring agents in cooking (Sharma, Gescher and Steward 2005). Recent research demonstrated that curcumin exhibits

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stupendous anti-cancer activity of various mechanisms with remarkable outcomes and minimum side effects. *In vitro* studies showed that curcumin acts as an anti-cancer agent by inducing cell apoptosis which results from the downregulation of anti-apoptotic proteins such as B-cell lymphoma 2 (Bcl-2) and upregulation of pro-apoptotic proteins (Li *et al*. 2017; Zhu and Bu 2017). Besides, *in vitro* study also demonstrates that curcumin is a chemosensitiser which could overcome chemoresistance and increases the sensitivity of malignant cells to chemotherapeutic agents such as doxorubicin (Wen *et al*. 2019).
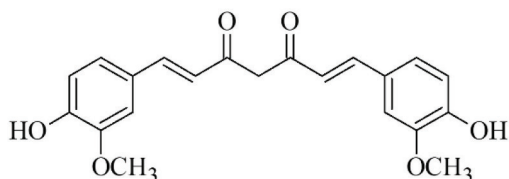

Figure 1: Chemical structure of curcumin.

Although curcumin shows tremendous versatility as a phytochemical molecule, several pharmacokinetic limitations hold back the application of curcumin in clinical settings. Firstly, several *in vivo* animal studies have shown that curcumin has limited absorption from the gastrointestinal tract following oral administration due to its poor aqueous solubility (Ravindranath and Chandrasekhara 1981; Wahlström and Blennow 2009). Moreover, clinical studies with human subjects justified the poor absorption of curcumin as a very limited concentration of curcumin is detected in the plasma distribution, regardless of the administered dose (Cheng 2001; Shoba *et al*. 1998). This observation was also reported in a clinical study which revealed that curcumin attains transient peak concentration since it rapidly decreases after 30 minutes of oral administration due to extensive metabolic reaction (Vareed *et al*. 2008). Therefore, the poor bioavailability of curcumin is due to a very limited concentration of curcumin is absorbed in the intestinal mucosa and it rapidly undergoes first-pass metabolism in the liver and excreted through faeces and urine (Anand *et al*. 2007; Esatbeyoglu 2012).

A self-microemulsifying drug delivery system (SMEDDS) is an isotropic mixture composed of surfactant, co-surfactant and lipid, which then forms oil-in-water (*o/w*) microemulsions upon mild agitation following the addition of the aqueous medium. SMEDDS is a lipid-based formulation of a drug delivery system with a promising approach to enhance the poor aqueous solubility and oral bioavailability of lipophilic drugs (Maurya 2017; Patel *et al*. 2010). Firstly, SMEDDS does not contain an aqueous medium during storage and before administration, therefore, this increases the stability and shelf-life upon long-term storage (Dokania and Joshi 2015). Moreover, SMEDDS formulations form microscopic droplets upon administration which helps to transport the drug rapidly from the stomach along the gastrointestinal tract to improve absorption, bioavailability and volume of distribution. Besides, it also helps to protect the gastrointestinal tract from drugs which may cause irritation due to prolonged contact (Tang, Sun and He 2007). Above all, SMEDDS formulations exhibit a constant therapeutic drug plasma concentration as it by-passes the first-pass metabolism and show good oral bioavailability (Narang, Delmarre and Gao 2007).

In this research, microemulsions were optimised by adjusting different ratios of surfactant (Tween 80), co-surfactant (PEG 400) and oil phase (palm oil). Surfactant (Tween 80), co-surfactant (PEG 400) and oil phase (palm oil), where they were purchased from Alfa Aesar (Lancashire, United Kingdom), ChemPur (Petaling Jaya, Malaysia) and Bendosen

(Petaling Jaya, Malaysia), respectively. Then, curcumin was loaded into the optimised microemulsions and the stability and characteristics of curcumin microemulsions were evaluated.

MATERIALS AND METHODS

Pre-Formulation Study of Microemulsion

Pre-concentrates (F1–F15) were prepared with Tween 80 as a surfactant, PEG 400 as the co-surfactants, palm oil as a lipid phase based on mass ratios obtained from their respective densities. The pre-concentrates were formulated by stirring of PEG 400 and Tween 80 until a homogeneous solution is obtained. Palm oil was added dropwise in the mixture in their respective ratios (Table 1). The stability of the mixtures which form stable pre-concentrates after storing overnight is added with distilled water at a 1:10 ratio (Basheer, Noordin and Ghareeb 2013; Sahu and Bothara 2015a; Shahu, Wadetwar and Dixit 2013). Samples which are appeared to be transparent and monophasic is identified as having capabilities in forming self-microemulsification (Wu *et al*. 2011) and they are used in formulation of curcumin microemulsion (Basheer, Noordin and Ghareeb, 2013). Ternary phase diagram was constructed using the ratios of surfactant, co-surfactant and oil which form stable pre-concentrates after storing overnight with addition of distilled water.

Table 1: Composition of pre-concentrates prepared in pre-formulation study and construction of phase diagram.

Formulation	Ratio		
	Tween 80	Palm oil	PEG 400
F1	8	1	1
F2	7	1	2
F3	7	2	1
F4	6	1	3
F5	6	2	2
F6	6	3	1
F7	5	1	4
F8	5	2	3
F9	5	3	2
F10	5	4	1
F11	4	1	5
F12	4	2	4
F13	4	3	3
F14	4	4	2
F15	4	5	1

Percentage of Transmittance Test

Percentage of transmittance values is used to determine the transparency for those pre-concentrates which has a clear appearance and without any phase separations. 100 µL of samples were withdrawn and diluted with distilled water at a 1:100 ratio and vortexed. The clarity of the samples were measured by ultraviolet-visible (UV-vis) (Perkin Elmer Lambda 25) spectrophotometer at 650 nm (Thakkar *et al.* 2011).

Solubility of Curcumin in Water, Oil, Surfactant and Co-surfactant

Curcumin powder was added in excess in a fixed volume of distilled water, palm oil, Tween 80 and PEG 400, respectively. The mixtures were allowed to stir overnight at room temperature and the samples were centrifuged at 2,000 rpm for 15 min. The samples were filtered and diluted within the range of the calibration curve. The concentration of curcumin in each vehicle was determined by measuring the absorbance using UV-vis spectrophotometer at 425 nm (Kadam *et al*. 2018; Shahu, Wadetwar and Dixit 2013).

Formulation of Curcumin Microemulsion

Firstly, 10 mg of curcumin powder was loaded into 1 mL of palm oil and the mixture was stirred overnight under room temperature until the curcumin powder was completely dissolved. The curcumin loaded palm oil were added to Tween 80 and PEG 400 based on their respective mass ratios and stirred overnight. The mixture was filtered using 0.45 µm millipore membrane filter and 1 mL of the sample was withdrawn and added into the distilled water at a 1:10 ratio. A stable monophasic formulations obtained is identified as microemulsion. A transparent and monophasic optimised appearance will be proceeded to the further tests whereas the cloudy and biphasic products were not entertained (Moghimipour, Salimi and Eftekhari 2013; Sharma *et al*. 2018).

Percentage of Curcumin Content in Microemulsion

The concentration of curcumin in microemulsions were determined through analysis of linear regression in calibration curve by using the UV-vis spectrometer at 425 nm. Each sample was diluted with 99% alcohol which is in the linearity range of the calibration curve. This test was performed in three replicates for each sample (Sahu and Bothara 2015b; Yadav *et al*. 2018).

pH Measurement of Curcumin Microemulsion

pH values were determined for both sets of microemulsions, which is before and after curcumin loading. Samples which exhibit higher percentage of transmittance were chosen to determine their pH values at room temperature, 25°C using digital pH meter with combined glass calomel electrode (CyberScan pH 510, Thermo Scientific) (Shahu, Wadetwar and Dixit 2013).

Thermodynamic Stability Test: Centrifugation

Centrifugation test was carried out using centrifuge (Heraeus Pico 17, Thermo Scientific) to identify a metastable formulation. One mL of optimised microemulsions were transferred into individual Eppendorf tubes. The samples were allowed to centrifuge at 3,500 rpm for 30 min. This test was performed for both microemulsions, before and after curcumin loading (Yadav *et al*. 2018).

RESULTS AND DISCUSSION

Self-Emulsification of Pre-Concentrates

The ternary phase diagram's shaded region remarks the self-microemulsifying region of the formulations upon incorporating the aqueous phase (Figure 2). A co-surfactant is an organic solvent which plays a vital role in microemulsions to reduce the interfacial tension between different phases and improves the stability of the formulations. A microemulsion should ideally has ultralow interfacial tension to sustain its stability upon a long-term shelf life (Maurya *et al*. 2017). Among the 15 formulations, there were 5 formulations (F1, F2, F4, F7 and F10) that are found to be stable, where there has no phase separation after storing overnight. Results demonstrated that to produce an efficient self-microemulsifying region, the amount of surfactant and co-surfactant which ranged between 50%–80% and 10%–40%, respectively is sufficient to reduce the interfacial tension as well to increase the transmittance value (Kim *et al*. 2019; Thakkar and Shah 2017). Here, a high amount of surfactant is required to emulsify palm oil due to the fact that palm oil contains long-chain triglycerides which possess poor self-microemulsifying properties as the result from the large hydrophobic portion in the molecule (Gurram *et al*. 2015). Nevertheless, pre-clinical studies demonstrated that the characteristics of different types of triglycerides (medium or long-chain triglycerides) did not showed significant influences in the absorption and bioavailability of drugs although it effects the self-microemulsification properties (Grove *et al*. 2006; Khoo *et al*. 1998; Porter *et al*. 2004).

Self-emulsification method is essential to study the characteristics of the formulation after incorporating the aqueous phase. This method typically mimics the *in vivo* environment once the pre-concentrates reaches the gastrointestinal tract to form microemulsion (Baek *et al*. 2013). The microemulsions that appear to be between transparent and translucent indicates that the drug is not likely to form precipitation when it reaches the gut (Kadam *et al*. 2018). Figure 3 shows that F1 appeared to be clear and the remaining samples (F2, F4, F7 and F10) were translucent.
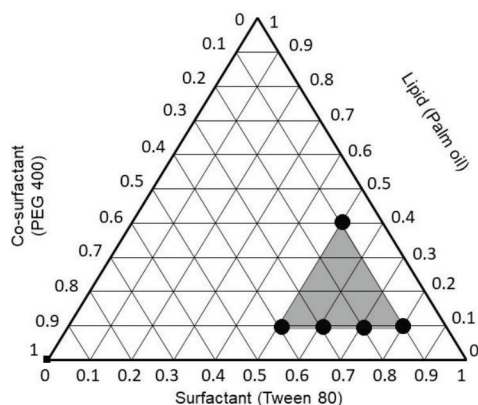
Figure 2: Pseudoternary phase diagrams for formulas, where the shaded region represent the self-emulsification region.
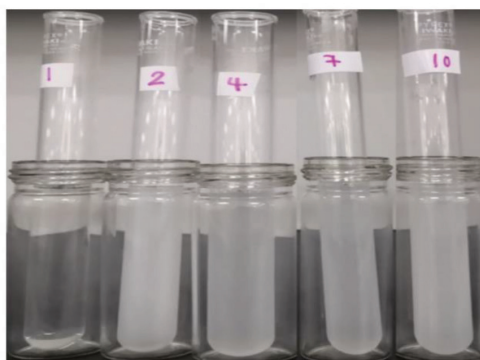

Figure 3: Visual observation of microemulsion after addition of water for F1, F2, F4, F7 and F10.

Transmittance value is a more systematic measure of transparency for microemulsion formulation compared to visual inspection. A 100-times dilution was carried out in this test to keep curcumin remain solubilised in the *in vivo* gastric environment (Czajkowska-Kośnik *et al*. 2015). Table 2 shows that F1 has the highest transmittance value which is about 100% which indicates the ideal transparency of microemulsion. The transmittance value of a formulation should be > 90% to justify it as a microemulsion (Thakkar *et al*. 2011). Therefore, F2 and F7 has the desired value of transmittance which is 97.73% and 91.70%, respectively. Meanwhile, F10 has a transmittance value of 86.47%, which is close to 90%. Thus, F7 was considered to be evaluated in further tests. However, F4 is incompliant to the characteristic of microemulsion as the percentage of transmittance is 61.6%, thus, it is identified as an emulsion (Thakkar *et al*. 2011). Hence, F4 was eliminated from this point of test.

Table 2: Percentage of transmittance value for the respective formulations. Data were obtained from at least three independent experiments.

Formulation	Percentage of transmittance
F1	100.70 ± 1.13
F2	97.70 ± 1.10
F4	61.60 ± 0.29
F7	91.70 ± 0.32
F10	86.47 ± 0.46

Solubility of Curcumin in Water, Oil, Surfactant and Co-Surfactant

Appropriate vehicles in active substances should possess a good solubilising property to serve a maximum drug transport capacity in SMEDDS (Sahu and Bothara 2015b). Besides, a promising solubility in the vehicles is important to prevent any precipitation of curcumin during the period of shelf-life or in the lumen of gastrointestinal tract after administration (Sahu and Bothara 2015a). Therefore, solubility study is important to identify the maximum capacity of every vehicles to solubilise curcumin and transport in SMEDDS.

As referring to Table 3, curcumin is most soluble in the surfactant, Tween 80, (30.11 ± 4.68) mg/mL and followed by the co-surfactant, PEG 400 (7.78 ± 1.43) mg/mL and palm oil (0.75 ± 0.11) mg/mL. The solubility of curcumin in water is < 0.1 mg/mL and it agrees well with previous study (0.0030 ± 0.001) mg/mL (Baek *et al*. 2013). The aqueous solubility of curcumin is very poor, thus, it requires modification in the transport system as an oral delivery drug. Tween 80 is structurally rich in hydroxyl (-OH) functional group which increases the solubility of curcumin by forming hydrogen bonds with the -OH groups and hydrogen atoms presented in curcumin (Baek *et al*. 2013).

Table 3: Concentration of curcumin solubility in different vehicles. Data were obtained from at least three independent experiments.

Solubility of curcumin	Concentration (mg/mL)
Distilled water	0.0030 ± 0.002
80% Tween 80	30.11 ± 4.68
80% PEG 400	7.78 ± 1.43
Palm oil	0.75 ± 0.11

Formulation of Curcumin Loaded Microemulsion

Curcumin loading into the microemulsions (F1, F2, F7 and F10) is one of the key objectives of this study. Referring to Figure 4, F1 and F2 appears clear and monophasic which exhibit a good microemulsion characteristics. Whereas, F7 and F10 forms milky solution that indicate formation of a simple emulsion, hence, F7 and F10 were eliminated from the study as it theoretically formed larger diameter of particle size and turned thermodynamically unstable.
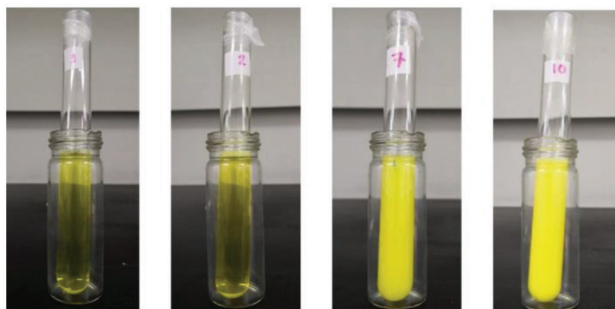
Figure 4: Visual observation of curcumin loaded microemulsions after addition of distilled water.

Percentage of Drug Content in Microemulsion

Percentage of curcumin content in microemulsion F1 and F2 were (97.78 ± 1.02)% and (87.46 ± 6.73)%, respectively (Table 4). Whereby, F1 exhibit the highest percentage of curcumin content which is nearly 100% and although F2 has a high percentage of content, but it is significantly further from 100%. Therefore, F1, demonstrates the chemical stability of curcumin in the microemulsion (Sahu and Bothara 2015a). Moreover, this also proves that although both formulations have the same amount of oil content, but surfactant influences the chemical stability of microemulsion after curcumin loading as the content of surfactant in F1 is higher than F2. Surfactant increases permeability of a drug into the intestinal membranes by improving affinity between oil phase and membranes. Hence, surfactant facilitates intestinal absorption of drugs by accelerating the dissolution rate and eventually enhances the solubility and bioavailability of a drug (Gursoy and Benita, 2004)

Table 4: Concentration and percentage of curcumin content in the optimised microemulsions.

Code	Concentration of curcumin (mg/mL)	Drug content (%)	pH
F1	0.73 ± 0.008	97.78 ± 1.02	6.92 ± 0.08
F2	0.66 ± 0.05	87.46 ± 6.73	6.91 ± 0.15

pH Measurement of Curcumin Microemulsions

pH measurement of curcumin microemulsion is essential to determine if the drug still remains within the oil phase. Curcumin is alkaline in nature, thus, when it diffused into the continuous phase (water), the pH value would be > 7. Inversely, if curcumin stays within the oil phase, the pH would be ~7, which shows the pH of water (Thakkar and Shah 2017). As discussed earlier, the *o/w* microemulsion is ideally desired to enhance the solubility of poor aqueous soluble drug. Therefore, curcumin will be loaded in the oil phase and it is important to ensure that it does not diffuse into the continuous phase. Referring to Table 4, the pH of F1 and F2 were 6.92 ± 0.08 and 6.91 ± 0.5; respectively and they are satisfactory because an oral delivery drug should be a unionised weak acid to get absorbed instantaneously in strong acidic medium, which is the gastric mucosa (Vertzoni *et al*. 2019). The pH range which is near to neutral shows the pH of water which composed the whole external phase as curcumin is remained in the dispersed phase (Thakkar and Shah 2017).

Thermodynamic Stability Test

Thermodynamic stability needs to be assessed more crucially in microemulsion as it determines the shelf-life capacity of the formulations. A formulation which appears to be a homogenous and clear indicates a good microemulsion, whereas, if it appeared to be cloudy and separated in phases which indicates the formation of a simple emulsion, and it is thermodynamically unstable (Kadam *et al*. 2018). F1 and F2 endured in a homogenous phase with clear appearance. This reflects both F1 and F2 are thermodynamically stable and serve its purpose to enhance the solubility of curcumin with a quality shelf-life.

CONCLUSION

Optimisation of curcumin microemulsions (F1–F15) were carried out by using different ratio of palm oil, surfactant (Tween 80) and co-surfactant (PEG 400). This was further proven through characterisation of SMEDDS whereby self-emulsification and percentage of transmittance study shows that F1, F2, F7 and F10 produced a transparent, monophasic and self-microemulsification at concentration of surfactant > 50% and co-surfactant < 40%. Once optimised pre-concentrates were acquired, optimisation of curcumin microemulsion was performed. The characterisation of curcumin SMEDDS was assessed with percentage of curcumin content and pH measurement, to identify the most compactible microemulsion formulations to enhance the solubility and bioavailability of curcumin. Furthermore, the evaluation of microemulsion stability showed satisfactory outcome in centrifugation test for F1 and F2, however, F7 and F10 are unable to retain the stability when a high intensity of physical agitation was introduced. The results suggested that F1 with 80% of Tween 80 content exhibits good characteristics of microemulsion to improve the physiochemical properties and shelf-life of curcumin as it produces a stable microemulsion with transparent and monophasic appearance that is compactible to all the characteristic tests with highest percentage of curcumin content.

REFERENCES

ANAND, P., KUNNUMAKKARA, A. B., NEWMAN, R. A. & AGGARWAL, B. B. (2007) Bioavailability of curcumin: Problems and promises, *Molecular Pharmaceutics* 4(6): 807–818. https://doi.org/10.1021/mp700113r

BAEK, M. K., LEE, J. H, CHO, Y. H, KIM, H. H. & LEE, G. W. (2013) Self-microemulsifying drug delivery system for improved oral bioavailability of pranlukast hemihydrate: Preparation and evaluation, *International Journal of Nanomedicine*, 8(1): 167–176. https://doi.org/10.2147/IJN.S37338

BASHEER, H. S., NOORDIN, M. I. & GHAREEB, M. M. (2013) Characterization of microemulsions prepared using isopropyl palmitate with various surfactants and cosurfactants, *Tropical Journal of Pharmaceutical Research*, 12(3): 305–310. https://doi.org/10.4314/tjpr.v12i3.5

CHENG, A. L., HSU, C. H., LIN, J. K., HSU, M. M., HO, Y. F., SHEN, T. S. *et al*. (2001) Phase I clinical trial of curcumin, a chemopreventive agent, in patients with high-risk of pre-malignant lesion, *Anticancer Research*, 21(4): 2895–2900.

CZAJKOWSKA-KOŚNIK, A., SZEKALSKA, M., AMELIAN, A., SZYMAŃSKA, E. & WINNICKA, K. (2015) Development and evaluation of liquid and solid self-emulsifying drug delivery systems for atorvastatin, *Molecular Diversity Preservation International*, 20(12): 21010–21022. https://doi.org/10.3390/molecules201219745

DOKANIA, S. & JOSHI, A. K. (2015) Self-microemulsifying drug delivery system (SMEDDS): Challenges and road ahead, *Drug Delivery*, 22(6): 675–690. https://doi.org/10.3109/107175 44.2014.896058

ESATBEYOGLU, T., HUBBE, P., ERNEST, I. M. A., CHIN, D., WAGNER, A. E. & RIMBACH, G. (2012) Curcumin-From molecule to biological function, *Angewandte Reviews*, 51(22): 5308–5332. https://doi.org/10.1002/anie.201107724

GURRAM, A. K., DESHPANDE, P. B., KAR, S. S., USHA, Y. N., UDUPA, N. & REDDY, M. S. (2015) Role of components in the formation of self-microemulsifying drug delivery systems, *Indian Journal of Pharmaceutical Sciences*, 77(3): 249–257. https://doi.org/10.4103/0250-474X.159596

GURSOY, N. & BENITA, S. (2004) Self-emulsifying drug delivery systems (SEDDS) for improved oral delivery of lipophilic drugs, *Biomedicine & Pharmacotherapy*, 58(3): 173–182. https://doi.org/10.1016/j.biopha.2004.02.001

GROVE, M., MÜLLERTZ, A., NIELSEN, J. L. & PEDERSEN, G. P. (2006) Bioavailability of seocalcitol: II: Development and characterisation of self-microemulsifying drug delivery systems (SMEDDS) for oral administration containing medium and long chain triglycerides, *European Journal of Pharmaceutical Sciences*, 28(3): 233–242. https://doi.org/10.1016/j.ejps.2006.02.005

KADAM, P. V., YADAV, K. N., BHINGARE, C. L. & PATIL, M. J. (2018) Standardization and quantification of curcumin from Curcuma longa extract using UV visible spectroscopy and HPLC, *Journal of Pharmacognosy and Phytochemistry*, 7(5): 1913–1918.

KHOO, S. M., HUMBERSTONE, A. J., PORTER, C. J. H., EDWARDS, G. A. & CHARMAN, W. N. (1998) Formulation design and bioavailability assessment of lipidic self-emulsifying formulations of halofantrine, *International Journal of Pharmaceutics*, 167(1): 155–164. https://doi.org/10.1016/S0378-5173(98)00054-4

KIM, D. S., CHO, J. H., PARK, J. H., KIM, J. S., SONG, E. S., KWON, J. *et al.* (2019) Self-microemulsifying drug delivery system (SMEDDS) for improved oral delivery and photostability of methotrexate, *International Journal of Nanomedicine*, 14(1): 4949–4960. https://doi.org/10.2147/IJN.S211014

LI, W., ZHOU, Y., YANG, J., LI, H., ZHANG, H. & ZHENG, P. (2017) Curcumin induces apoptotic cell death and protective autophagy in human gastric cancer cells, *Oncology Reports*, 37(6): 3459–3466. https://doi.org/10.3892/or.2017.5637

MAURYA, S., ARYA, R., RAJPAL, G. & DHAKAR, R. C. (2017) Self-micro emulsifying drug delivery system (SMEDDS): A review on physio-chemical and biopharmaceutical aspects, *Journal of Drug Delivery and Therapeutics*, 7(3): 55–65. https://doi.org/10.22270/jddt.v7i3.1453

MOGHIMIPOUR, E., SALIMI, A. & EFTEKHARI, S. (2013) Design and characterization of microemulsion systems for naproxen, *Advanced Pharmaceutical Bulletin*, 3(1): 63–71.

NARANG, A. S., DELMARRE, D. & GAO, D. (2007) Stable drug encapsulation in micelles and microemulsions, *International Journal of Pharmaceutics*, 345(1–2): 9–25. https://doi.org/10.1016/j.ijpharm.2007.08.057

PATEL, J. M., PATEL, S. S., PATEL, M. N. & PATEL, M. M. (2010) A self-microemulsifying drug delivery system (SMEDDS), *International Journal of Pharmaceutical Sciences Review and Research*, 4(3): 29–35.

PORTER, C. J. H., KAUKONEN, A. M., BOYD, B. J., EDWARDS, G. A. & 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. https://doi.org/10.1023/B:PHAM.0000036914.22132.cc

PRIYADARSINI, K. (2014) The chemistry of curcumin: From extraction to therapeutic agent, *Molecules*, 19(12): 20091–20112. https://doi.org/10.3390/molecules191220091

RAVINDRANATH, V. & CHANDRASEKHARA, N. (1981) Metabolism of curcumin-studies with [3H] curcumin, *Toxicology*, 22(4): 337–344. https://doi.org/10.1016/0300-483X(81)90027-5

SAHU, A. R. & BOTHARA, S. B. (2015a) Design and development of self-microemulsifying drug delivery system of curcumin by simplex lattice design, *Semantic Scholar*, 4(2): 73–80.

SAHU, A. R. & BOTHARA, S. B. (2015b) Formulation and evaluation of self-microemulsifying drug delivery system of curcumin for enhanced solubility and dissolution, *Asian Journal of Pharmaceutical Education and Research*, 4(1): 48–59.

SHAHU, S. G., WADETWAR, R. N. & DIXIT, G. R. (2013) Development of microemulsion for solubility enhancement of poorly water-soluble drug valsartan, *International Journal of Pharmaceutical Sciences Review and Research*, 22(2): 246–251.

SHARMA, R. A., GESCHER, A. J. & STEWARD, W. P. (2005) Curcumin: The story so far, *European Journal of Cancer*, 41(13): 1955–1968. https://doi.org/10.1016/j.ejca.2005.05.009

SHARMA, S., GANJU, E., UPMANYU, N. & JAIN, P. (2018) Therapeutic microemulsion of curcumin for the management of osteoarthritis, *Journal of Drug Delivery and Therapeutics*, 8(5): 341–347. https://doi.org/10.22270/jddt.v8i5-s.1989

SHOBA, G., JOY, D., JOSEPH, T., MAJEED, M., RAJENDRAN, R. & SRINIVAS, P. (1998) Influence of piperine on the pharmacokinetics of curcumin in animals and human volunteers, *Planta Medica*, 64(4): 353–356. https://doi.org/10.1055/s-2006-957450

TANG, J. L., SUN, J. & HE, Z. G. (2007) Self-emulsifying drug delivery systems: Strategy to improve oral delivery of poorly soluble drugs, *Current Drug Therapy*, 2(1): 85–93. https://doi.org/10.2174/157488507779422400

THAKKAR, H., NANGESH, J., PARMAR, M. & PATEL, D. (2011) Formulation and characterization of lipid-based drug delivery system of raloxifene-microemulsion and self-microemulsifying drug delivery system, *Journal of Pharmacy and Bioallied Sciences*, 3(3): 442. https://doi.org/10.4103/0975-7406.84463

THAKKAR, V. & SHAH, A. (2017) Optimization of self-microemulsifying drug delivery system containing curcumin and artemisinin using D-optimal mixture design, *Saudi Journal of Medical and Pharmaceutical Sciences*, 3(5): 388–398.

VAREED, S. K., KAKARALA, M., RUFFIN, M. T., CROWELL, J. A., NORMOLLE, D. P., DJURIC, Z. *et al*. (2008) Pharmacokinetics of curcumin conjugate metabolites in healthy human subjects, *American Association for Cancer Research*, 17(6); 1411–1417. https://doi.org/10.1158/1055-9965.EPI-07-2693

VERTZONI, M., AUGUSTIJNS, P., GRIMM, M., KOZIOLEK, M., LEMMENS, G., PARROTT, N. *et al*. (2019) Impact of regional differences along the gastrointestinal tract of healthy adults on oral drug absorption: An UNGAP review, *European Journal of Pharmaceutical Sciences*, 134: 153–175. https://doi.org/10.1016/j.ejps.2019.04.013

WAHLSTRÖM, B. & BLENNOW, G. (2009) A study on the fate of curcumin in the rat, *Acta Pharmacologica et Toxicologica*, 43(2): 86–92. https://doi.org/10.1111/j.1600-0773.1978.tb02240.x

WU, X., XU, J., HUANG, X. & WEN, C. (2011) Self-microemulsifying drug delivery system improves curcumin dissolution and bioavailability, *Drug Development and Industrial Pharmacy*, 37(1): 15–23. https://doi.org/10.3109/03639045.2010.489560

WEN, C., FU, L., HUANG, J., DAI, Y., WANG, B., XU, G., WU, L. & ZHOU, H. (2019) Curcumin reverses doxorubicin resistance via inhibition the efflux function of ABCB4 in doxorubicinresistant breast cancer cells, *Molecular Medicine Reports*, 19(6): 5162–5168. https://doi.org/10.3892/mmr.2019.10180

YADAV, V., JADHAV, P., KANASE, K., BODHE, A. & DOMBE, S. (2018) Preparation and evaluation of microemulsion containing antihypertensive drug, *International Journal of Applied Pharmaceutics*, 10(5): 138–146. https://doi.org/10.22159/ijap.2018v10i5.27415

ZHU, Y. & BU, S. (2017) Curcumin induces autophagy, apoptosis, and cell cycle arrest in human pancreatic cancer cells, *Evidence-Based Complementary and Alternative Medicine*, 2017: 1–13. https://doi.org/10.1155/2017/5787218