Indo Global Journal of Pharmaceutical Sciences, 2020; 10(1): 33-42

INDO GLOBAL JOURNAL OF PHARMACEUTICAL SCIENCES
ISSN 2249- 1023

Nanoemulsion System for Improvement of Raspberry Ketone Oral Bioavailability

Sangeeta Singh [1], Tarun Virmani [1], Kanchan Kohli [2*]

[1] *School of Pharmaceutical Sciences, MVN University, Palwal, Haryana, India*

[2] *Department of Pharmaceutics, SPER, Jamia Hamdard, New Delhi, India*

Address for Correspondence: Kanchan Kohli, kkohli@jamiahandard.ac.in , kanchankohli@gmail.com

Received: 11.06.2020
Accepted: 01.07.2020
Published: 31.10.2020

Keywords
Raspberry ketone, Nanoemulsion, Emulsification, Pharmacokinetic studies.

ABSTRACT: Raspberry ketone belongs to statin group. It exhibit anti-hyperlipidemic activity. The main drawback associated with raspberry ketone is its low oral bioavailability (less than 20 %) due to poor aqueous solubility. The objective of present work was to design a formulation to improve the solubility using nanooemulsion and to enhance the bioavailability of raspberry ketone by delivering it at the molecular level in the form of nanodroplets through oral route. Prepared formulation was studied for droplet size, polydispersity index (PDI), percentage transmittance, refractive index, viscosity, zeta potential, surface morphology by transmission electron microscopy (TEM) and in vitro release study. Pharmacokinetic studies were carried out using Wistar albino rats to evaluate plasma levels of raspberry ketone. Optimized formulation exhibited spherical droplets with average diameter of 68.30 ± 2.32 nm, PDI of 0.167 ± 0.055 and zeta potential values of -28.50 ± 0.12 mV. Prepared nanoemulsion exhibited good transmittance (99.50 ± 0.06 %), refractive index (1.40 ± 0.01) and viscosity (32.12 ± 1.40 cP). The AUC (0−24) for nanoemulsion formulation (32.692 ± 2.621 µg.h/ml) was significantly higher ($p < 0.05$) than raspberry ketone suspension (14.606 ± 1.516 µg.h/ml). The Cmax of raspberry ketone nanoemulsion and raspberry ketone suspension was found to be 3.501 ± 0.086 and 1.247 ± 0.067 µg/ml, respectively. The value of AUC and Cmax of nanoemulsion after oral administration were 2.2 fold and 2.8-fold higher than those of suspension, respectively. Higher value of AUC and Cmax in case of nanoemulsion ensured higher drug availability at the site of action. On the basis of these research findings, it was concluded that raspberry ketone loaded nanoemulsion could be a better option for improving its oral bioavailability.

Cite this article as: Singh, S.; Virmani, T.; Kohli, K. Nanoemulsion system for improvement of raspberry ketone oral bioavailability. Indo Global J. Pharm. Sci., 2020; 10(1): 33-42. **DOI**: http://doi.org/10.35652/IGJPS.2020.10105 .

INTRODUCTION

Raspberry is one of the oldest fruits. It is used for medicinal and nutritional purposes. It has been utilized throughout the centuries. Blueberry and strawberry are close relatives of raspberry. It is full of minerals, polyphenols, sugars and vitamins. One of the main constituent in raspberry is ellagic acid. It inhibits tumor inductions in esophagus, lungs and liver. Raspberry has a good flavor and fragrance. These are due to presence of several aromatic components. Raspberry ketone is (4-(4-hydroxyphenyl) butan-2-one). It is one of the main aromatic constituent of raspberry. It also has the function of anti-aging, anti-oxidation, hypoglycemic and so on [1].

Raspberry ketone has poor aqueous solubility thus poor bioavailability of 20%. Enhancement in dissolution rate of poorly water soluble drugs has been achieved by utilizing strategies like salt formation [2], use of co-solvents, surfactant [3, 4], reduction in particle size [5], microemulsion [6], self-emulsification [7], complexation, the pro-drug approach [8] and solid dispersion [9, 10]. Nanoemulsion is an isotropic system [11]. Nanoemulsion was selected as to enhance the oral bioavailability of raspberry ketone, as these systems require very simple and cheap manufacturing facilities [12]. Moreover, it provides various benefits over the conventional systems in terms of stability and quick onset of action.

MATERIALS AND METHODS

Materials

Raspberry ketone was gift sample from the Kshipra Biotech, Indore, India. Sefsol 218® was provided as gift sample from Nikko Chemicals (Tokyo, Japan). The oil vitamin E was purchased from Merck, Mumbai, India. Olive oil and almond oil were purchased from Falcon, Bengaluru (India). Linseed oil was purchased from Sigma-Aldrich, Mumbai, India. Solutol HS 15 was provided as gift samples from Signet Chemicals Corporation Pvt. Ltd, Mumbai, India. Tween 20, tween 60, tween 80 and polyethylene glycol 400 were gifted samples from SD Fine Chemicals, New Delhi, India. Propylene glycol was procured from Thomas Baker Chemicals, Mumbai, India.Capmul MCM, lauroglycol 90 and transcutol P were obtained as gift from Gattefosse (Saint Priest, Cedex, France). HPLC-grade acetonitrile was purchased from Merck, Mumbai, India.

Methods

1. Analytical methodology

Raspberry ketones were examined by HPLC method. HPLC equipped with quaternary LC-10A VP pumps. The detector utilized was UV/VIS detector SPD-10AVP. For analysis of raspberry ketones reversed-phase high-performance liquid chromatography (RP-HPLC) method was used. The mobile phase was a mixture of acetonitrile and methanol (60:40). The flow rate was 1.5 ml/min. Before analysis samples were filtered through nylon filter (pore size, 0.45 µm) and then degassed by sonication in an ultrasonic bath. Assays were performed at ambient temperature (25 ± 1 °C) by injecting a 20 µl of sample in HPLC system and fixing the wavelength of detector at 243 nm.

2. Selection of excipients

Solubility of raspberry ketone in various oils (Sefsol 218®, olive oil, linseed oil, vitamin E, almond oil and capmul MCM), surfactant (tween 20, tween 60, tween 80, Solutol HS), co-surfactant (lauroglycol 90, propylene glycol, propylene glycol 400, Transcutol P) was determined by adding an excess amount of raspberry ketone in 2 ml of the selected vehicles in 5 ml stopper vials and allowed to mix using vortex mixer. The vials were then kept at 27 ± 0.5ºC in an isothermal shaker for about 72 hours to reach to equilibrium. The samples were centrifuged at 3000 rpm for fifteen minutes. The supernatant was taken and the concentration of raspberry ketone was determined using HPLC method. Surfactant and co-surfactant were selected on the basis of miscibility with selected oil. Miscibility studies were performed by adding selected oil to surfactant or co-surfactant in 1:1 ratio. The system was shaken for about 10 min. These resulted mixtures were visually observed for clarity. Those mixtures which appeared clear were chosen.

3. Construction of pseudoternary phase diagram

Pseudoternary phase diagrams were plotted according to the procedure explained by Kumar and associates [13]. The purpose of constructing phase diagrams was to identify the ratio of surfactant and co-surfactant required to prepare nanoemulsion. Different ratios (1:0, 1:1, 2:1, 3:1, 4:1 and 1:2, 1:3) of surfactant and co-surfactant (S_{mix}) were used. Aqueous titration method was used to prepare pseudoternary phase diagram. Slow titration with water was carried out for all ratios of S_{mix} and oil. After each 5% addition of water to the volume ratio, visible observation was done. Those system which appeared transparent and easily flowable (nanoemulsion) were marked in was marked on a pseudo three component phase diagram representing the aqueous phase, second representing oil, and the last represent the S_{mix} at fixed ratio by using CHEMIX School software ver 3.60 (USA).

4. Formulation and optimization of nanoemulsion by experimental design

Table 1. Independent variables used in box-benkhen design.

Symbol	Independent variable	Levels		
		-1	0	1
X_1	Oil (%)	2.34	3.12	3.90
X_2	S_{mix} (%)	9.37	12.5	15.62
X_3	Homogenization pressure (bar)	1250	1500	1750
X_4	Number of homogenization cycles	6	8	10

A four factors, three levels BBD statistical design was selected to optimize silymarin loaded nanoemulsion. In present study a range of 2.34-3.90 % for oil, 9.37-15.62 % for S_{mix} and 1250-1750 bar for homogenization pressure were selected for optimization. The range of homogenization cycles was taken as 6-10. The constraints for droplet size was set at minimum whereas for percentage transmittance, zeta potential and drug release the constraints set at maximum. **Table 1** summarizes an account of the independent and dependent variables. Design Expert® software (Design Expert® 9.0.4.1, State-Ease Inc., Minneapolis, USA) was employed to evaluate the effects of oil, S_{mix} concentration, processing pressure and number of

cycles on the droplet size, zeta potential, % transmittance and percentage drug release. Several nanoemulsion formulations were prepared as per the design described in **Table 2** for various runs generated and were investigated for droplet size, zeta potential, transmittance and % drug release as the response variables.

Oil in water nanoemulsion loaded with raspberry ketone were prepared by high energy emulsification technique. Briefly, coarse emulsions (20 ml) were formulated by mixing oil, S_{mix}, water and raspberry ketone using vortex mixer. Nanoemulsions were prepared by passing coarse emulsions through a high pressure homogeniser (STANSTED® Pressure Cell Homogeniser, Harlow, Essex CM19 5FN, UK). The prepared nanoemulsions were evaluated for droplet size, transmittance, zeta potential and *in vitro* drug release. On the basis of constraint of dependent variables, optimized formulation was chosen by numerical technique with higher desirability factor. This optimized raspberry ketone loaded nanoemulsion was further used for *in vitro* and *in vivo* characterization.

5. Characterization of optimized formulation

5.1 Droplet size and PDI

Droplet size and size distribution (PDI) of optimized nanoemulsion was evaluated using Zetasizer (Zetasizer 1000 HAS, Malvern Instruments, UK) in triplicate.

5.2 Percentage transmittance

UV spectrophotometer (UV 1601 Shimadzu, Japan) was used to estimate percentage transmittance. Formulation (1 ml) was taken in cuvette and percentage transmittance was recored at 630 nm in triplicate.

5.3 Refractive index and viscosity

Refractive index was estimated using Abbe refractometer (Nirmal International, India) in triplicate. Viscosity was measured without dilution using a Brookfield DV III ultra V6.0 RV cone and plate viscometer (Brookfield Engineering Laboratories, MA). All the measurements were carried out at a temperature of 26 ± 0.5°C.

Table 2. Calculated values of transmittance (Y_1), droplet size (Y_2), zeta potential (Y_3) and % drug release (Y_4) of raspberry ketone nanoemulsion obtained from BBD (response value are represented as mean value)

Run	X_1	X_2	X_3	X_4	Y_1	Y_2	Y_3	Y_4
1	-1	-1	0	0	92.88	113.00	-26.50	51.18
2	1	-1	0	0	90.00	148.00	-25.60	50.00
3	-1	1	0	0	97.32	61.00	-35.00	86.00
4	1	1	0	0	96.00	70.00	-32.60	79.14
5	0	0	-1	-1	94.55	80.40	-30.00	66.02
6	0	0	1	-1	94.87	76.00	-30.50	67.42
7	0	0	-1	1	95.54	70.65	-31.70	78.20
8	0	0	1	1	97.18	61.83	-34.60	85.49
9	-1	0	0	-1	98.22	56.61	-35.80	86.50
10	1	0	0	-1	94.68	80.04	-30.00	66.34
11	-1	0	0	1	98.62	54.00	-36.30	88.87
12	1	0	0	1	95.12	74.03	-31.00	68.28
13	0	-1	-1	0	91.34	143.00	-25.80	50.32
14	0	1	-1	0	94.48	83.00	-29.50	63.89
15	0	-1	1	0	92.15	120.00	-26.20	50.97
16	0	1	1	0	99.75	45.60	-38.00	95.00
17	-1	0	-1	0	93.90	90.00	-28.70	55.35
18	1	0	-1	0	92.04	122.00	-26.00	50.75
19	-1	0	1	0	95.33	74.00	-31.30	68.75
20	1	0	1	0	93.77	97.40	-27.90	52.83
21	0	-1	0	-1	93.63	107.00	-27.20	52.00
22	0	1	0	-1	99.25	50.00	-36.90	92.39
23	0	-1	0	1	93.00	109.00	-26.10	51.88
24	0	1	0	1	99.00	50.40	-36.80	91.53
25	0	0	0	0	95.10	74.82	-30.10	68.25
26	0	0	0	0	95.43	74.36	-30.90	68.76
27	0	0	0	0	95.00	74.07	-31.00	69.15
28	0	0	0	0	94.94	73.97	-29.90	67.83
29	0	0	0	0	95.62	74.57	-30.80	68.00

Table 3. Solubility of raspberry ketone in oils, surfactants and co-surfactants and miscibility of selected oil with surfactants and co-surfactants

Solubility of raspberry ketones in oils		Solubility of raspberry ketonesin surfactants (S)/co-surfactant (C)		Miscibility of Sefsol 218® with surfactant/co-surfactant
Oil	Solubility (mg/ml) ± S.D. (n = 3)	Surfactant (S)/co-surfactant (C)	Solubility (mg/ml)±S.D. (n=3)	Observation
Sefsol 218®	65.43 ± 4.76	Tween 20 (S)	16.46 ± 2.32	Phase separation
Olive oil	9.05 ± 1.31	Tween 80 (S)	20.81 ± 2.70	Clear
Linseed oil	5.64 ± 0.56	Tween 60 (S)	12.02 ± 1.90	Phase separation
Vitamin E	13.23 ± 2.01	Solutol HS 15 (S)	8.21 ± 0.86	Turbid
Almond oil	11.50 ± 1.63	Lauroglycol 90 (C)	14.21 ± 1.35	Clear
Capmul MCM	10.60 ± 1.48	Propylene glycol (C)	11.03 ± 1.22	Phase separation
		Propylene glycol 400 (C)	10.44 ± 1.07	Phase separation
		Transcutol P (C)	9.71 ± 0.82	Phase separation

Table 4. Relative pharmacokinetic parameters of different formulations of raspberry ketone

Formulation	C_{max} (µg/ml) ± S.D.	T_{max} (h) ± S.D.	AUC_{0-24} (µg.h/ml) ± S.D.	Elimination Rate constant
Drug nanoemulsion	3.501 ± 0.086	2.00 ± 0.12	32.692 ± 2.621	0.075 ± 0.012
Drug suspension	1.247 ± 0.067	6.00 ± 0.43	14.606 ± 1.516	0.008 ± 0.001

5.4 Surface charge determination

Surface charge of nanoemulsion was estimated by measuring the electrophoretic mobility. Measurements were carried by zeta potential measuring equipment (Zetasizer-1000 HAS, Malvern Instruments, UK).

5.5 Surface morphology by transmission electron microscopy (TEM)

Optimized nanoemulsion was evaluated for surface morphology using Morgagni 268D transmission electron microscope (FEI, Hillsbro, Holand) operated at 70 kV. A drop of nanoemulsion was taken and deposited on a wax paper which was further stained with 2% (w/v) phosphotungstic acid and air dried. Slide was observed for surface morphology with TEM.

5.6 Drug content

Raspberry ketone content of prepared nanoemulsion was studied by diluting nanoemulsion suitably with ethanol and then raspberry ketone content was estimated using HPLC method. Determined raspberry ketone content was designated as percent of total amount of drug.

6. *In vitro* release studies using dialysis membrane

Release studies were performed to compare the release of raspberry ketone from nanoemulsion with raspberry ketone suspension. One milliliter of nanoemulsion (containing drug

60 mg/ml) and drug suspension were filled in dialysis bag which was tied using nylon thread. Release study was carried in 500 ml of phosphate buffer pH (7.4) solution using magnetic stirrer (Metrex, Delhi, India) operated at 100 rpm and 37 ± 0.5 ºC. At regular intervals (0, 30, 60, 90, 120,150, 180, 210, 240, 300 and 360 min) samples were withdrawn and replaced with fresh buffer. Samples were evaluated for raspberry ketone content using HPLC method at 243 nm.

7. Pharmacokinetic studies

Pharmacokinetic studies were carried out using Wistar albino rats to evaluate plasma levels of raspberry ketone. Animals were divided into two groups. All animal studies were performed out after approval of the protocol by Institutional Animal Ethics Committee. Formulations were given orally by using oral feeding cannula and micropipette. Group A was orally administered with raspberry ketone suspension at a dose of 11 mg per 250 gm weight of rat [14, 15] whereas group B received raspberry ketone nanoemulsion orally at a dose of 11 mg per 250 gm weight of rat. The rats were anesthetized using diethyl ether and blood samples (0.2 ml) were withdrawn from the retro-orbital eye vein of a rat at 0 (predose), 1, 2, 4, 6, 8 and 24 h. The samples were collected in EDTA coated micro centrifuge tubes. About 100 µl of phosphate buffer (pH 8) was added to 100 µl of each plasma sample, followed by agitation for 30 sec. Then, 2.5 ml of diethyl ether was added to the mixture and vortexed for 15 min. The mixture was then centrifuged at 1500 rpm for 5 min. After this 2ml of the organic phase was quantitatively transferred into fresh eppendorf tubes and vacuum pump evaporator was used to evaporate supernatant. The residues were resuspended in 100 µl of methanol and centrifuged at 9200 rpm for 10 min. From this mixture 20µl of the supernatant was analysed for raspberry ketone using HPLC (Shimadzu, Tokyo, Japan). The obtained data was used to determine various pharmacokinetic parameters of raspberry ketone.

Simple, sensitive and validated HPLC method was used for the determination of raspberry ketone in rat plasma. HPLC equipped with wavelength programmable UV/VIS detector SPD-10AVP, Rheodyne injector fitted with a 20 µl loop, Degasser DGU-14A, Controller SCL-10A VP and Indicator FCV-10AL VP was used. The concentration of raspberry ketone in plasma was evaluated by using a mixture of acetonitrile and methanol (60:40) as mobile phase. Phenomenex C_{18} column (150 × 4.6 mm, 5 µm in particle size; Hypersil, USA) was used for liquid chromatography separation, which was carried out at room temperature. The flow rate of mobile phase was 1.5 ml/min and retention time was 3 min. Raspberry ketone was analyzed spectrometrically at 243 nm. The internal standard was heptadecanoic acid [16].

RESULTS AND DISCUSSION

Selection of excipients

Amongst oils, raspberry ketone showed highest solubility (65.43 ± 4.76 mg/ml) in Sefsol 218® therefore this oil was selected as oil phase (**Table 3**). Amongst surfactants, raspberry ketone showed highest solubility in tween 80 (20.81 ± 2.70 mg/ml) in comparison to others. Results of miscibility study showed that tween 80 was miscible with sefsol 218®. On the basis of solubility and miscibility data, tween 80 was selected as surfactant as drug exhibited more solubility in it. Raspberry ketone showed highest solubility in lauroglycol 90 (14.21 ± 1.35 mg/ml) in comparison to other co-surfactants. Moreover, lauroglycol 90 showed miscibility with sefsol 218® on the basis of which it was selected as co-surfactant.

Pseudoternary phase diagram

Pseudoternary phase diagrams were plotted for each S_{mix} ratio (**Figure 1**). In S_{mix} ratio 1:1, the area of nanoemulsion was less as compared to the 2:1 ratio. In the case of S_{mix} 4:1 more area was observed as compared to the ratio 3:1 suggesting higher emulsification. In S_{mix} ratio 5:1 it was found that no further emulsification took place on addition of surfactant. Influence of enhanced content of co-surfactant with respect to surfactant (1:2 and 1:3) was also observed. It was found that on enhancing co-surfactant content there was reduction in nanoemulsion area.

Response analysis for optimization of nanoemulsion

Smaller the droplet size, more is the transmittance of nanoemulsion. ANOVA results showed that surfactant amount ($p<0.0001$) has the most significant effect on transmittance, followed by oil ($p<0.0001$), pressure ($p<0.0001$) and cycle ($p<0.05$). Percentage transmittance for prepared batches was in range of 90.00 to 99.75 % indicating that prepared nanoemulsion were transparent and clear. The interaction effect between different factors has been shown in **Figure 2** as three dimensional response surface plots. There was increase in transmittance with increase in S_{mix}, pressure and cycle.

Surfactant had a significant effect on droplet size of nanoemulsion with $p<0.0001$, followed by oil ($p<0.0001$), pressure ($p<0.0001$) and cycle ($p<0.05$). The mean droplet size of the prepared batches was in range of 45.60 to 148.00 nm (table 2). It was observed that droplet size of formulation increases with increase in oil content.

More the zeta potential value lead to decreased droplets coalescence. Surfactant has more effect on zeta potential of nanoemulsion with p<0.0001, followed by oil (p<0.0001), pressure (p<0.05) and cycle (p<0.05). Increment in drug release was observed with increase in surfactant concentration which might be due to ability of S_{mix} to reduce the droplet size.

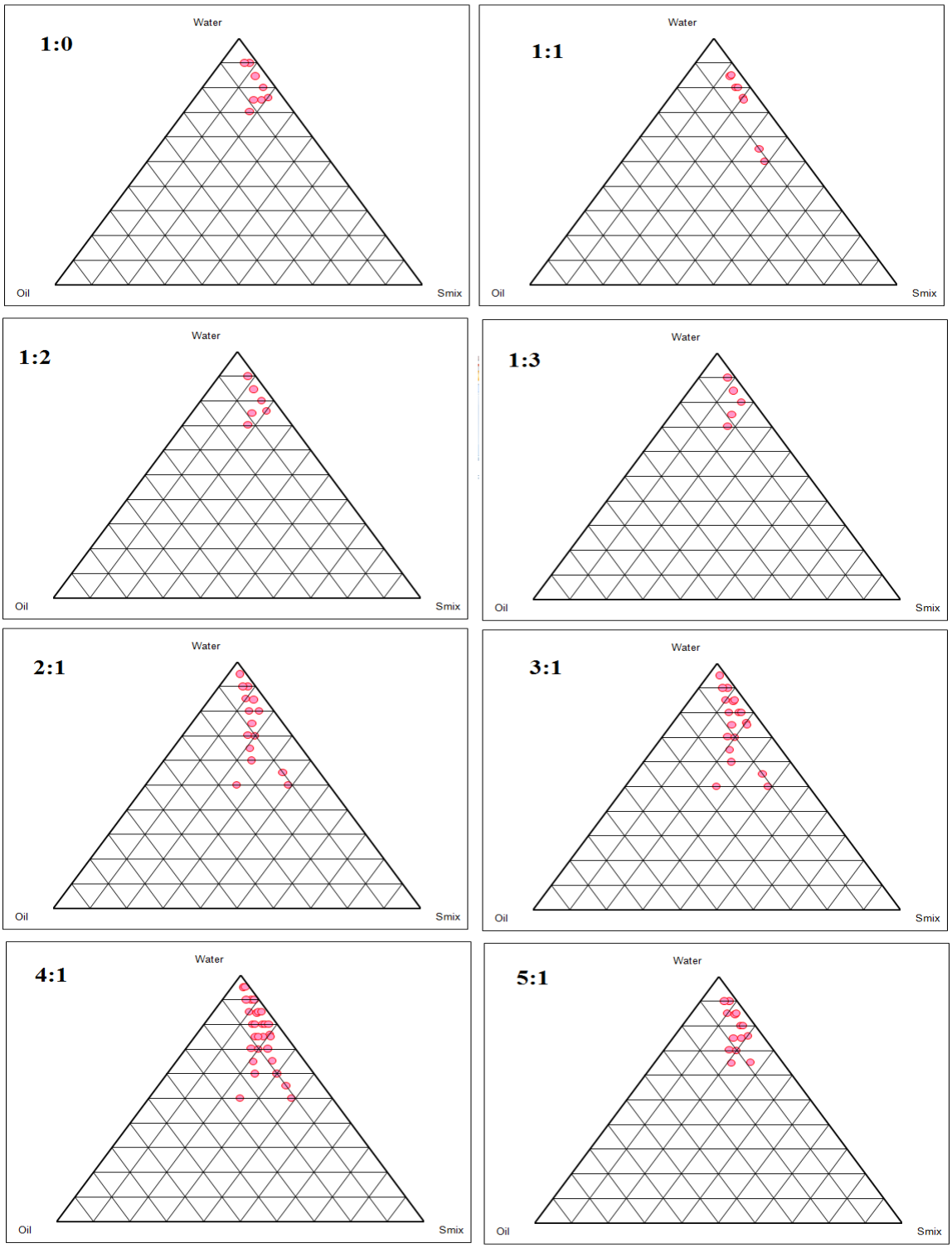

Figure 1. Pseudo ternary phase diagram showing existence of o/w nanoemulsion region for different surfactant: co-surfactant ratios (or S_{mix}). (a) 1:0; (b) 1:1; (c) 1:2; (d) 1:3; (e) 1:4; (f) 2:1; (g) 3:1; (h) 4:1 and (i) 5:1

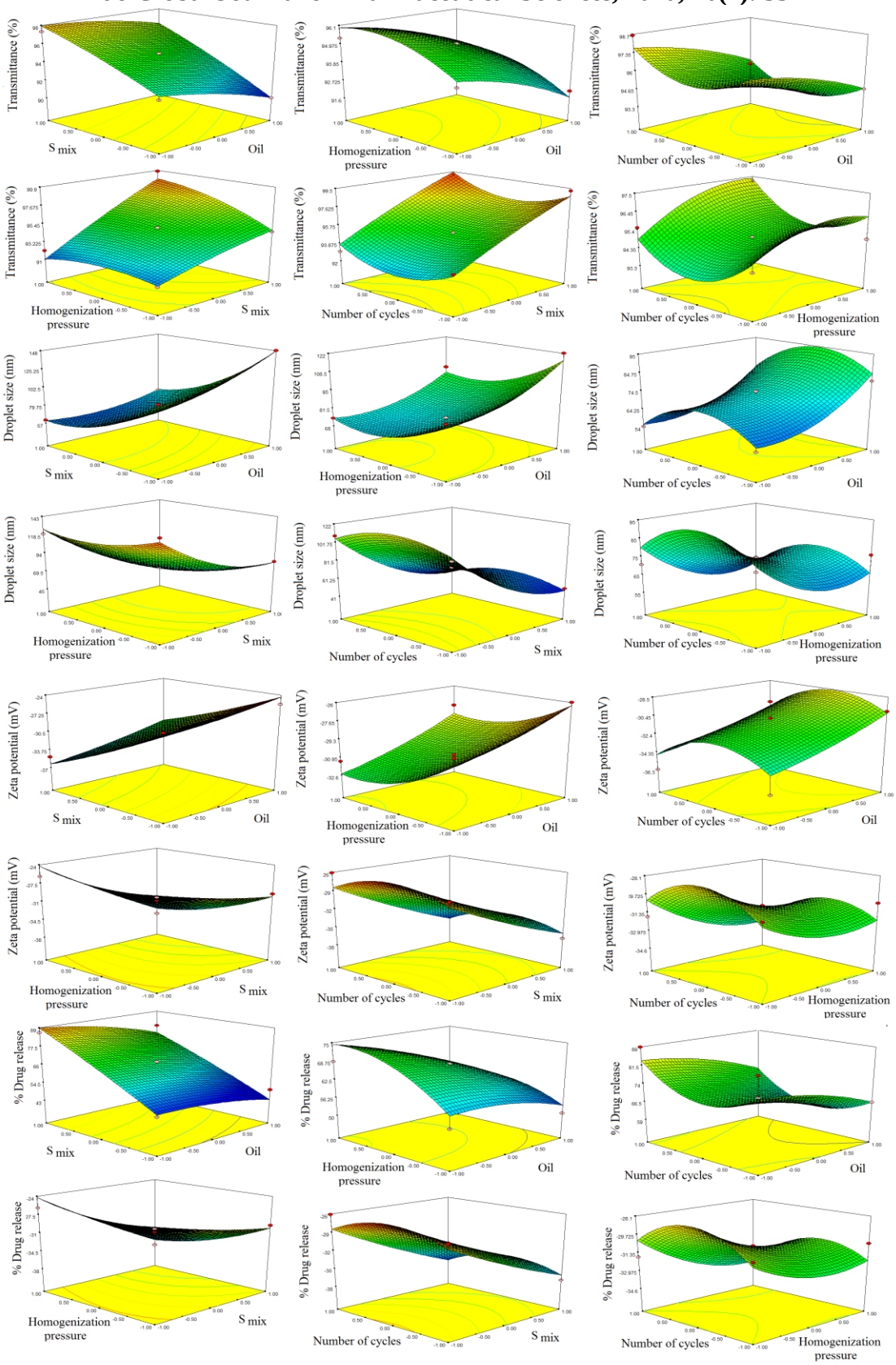

Figure 2. Response surface plots (BBD design) showing effect of different independent variables (oil, S_{mix}, homogenization pressure and number of homogenization cycles) on transmittance, droplet size, zeta potential and drug release of nanoemulsion

		Diam. (nm)	% Intensity	Width (nm)
Z-Average (d.nm): 68.3	Peak 1:	73.5	100.0	84.89
PdI: 0.167	Peak 2:	0.000	0.0	0.000
Intercept: 0.922	Peak 3:	0.000	0.0	0.000
Result quality : Good				

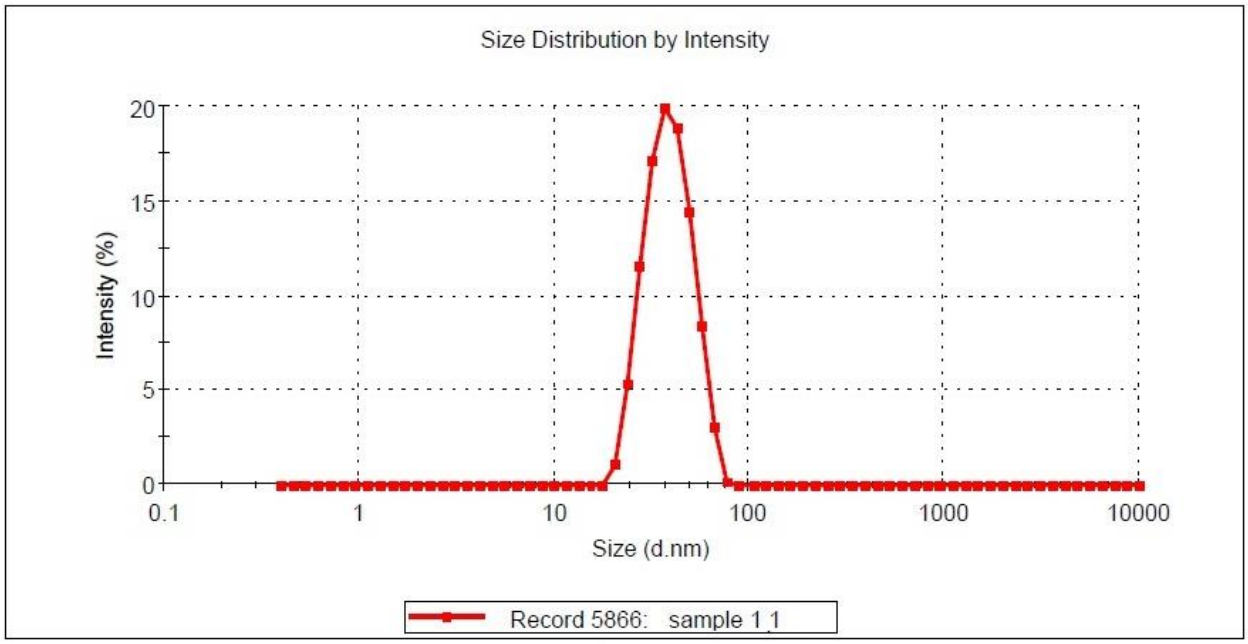

Figure 3. Droplet size and PDI value of formulation

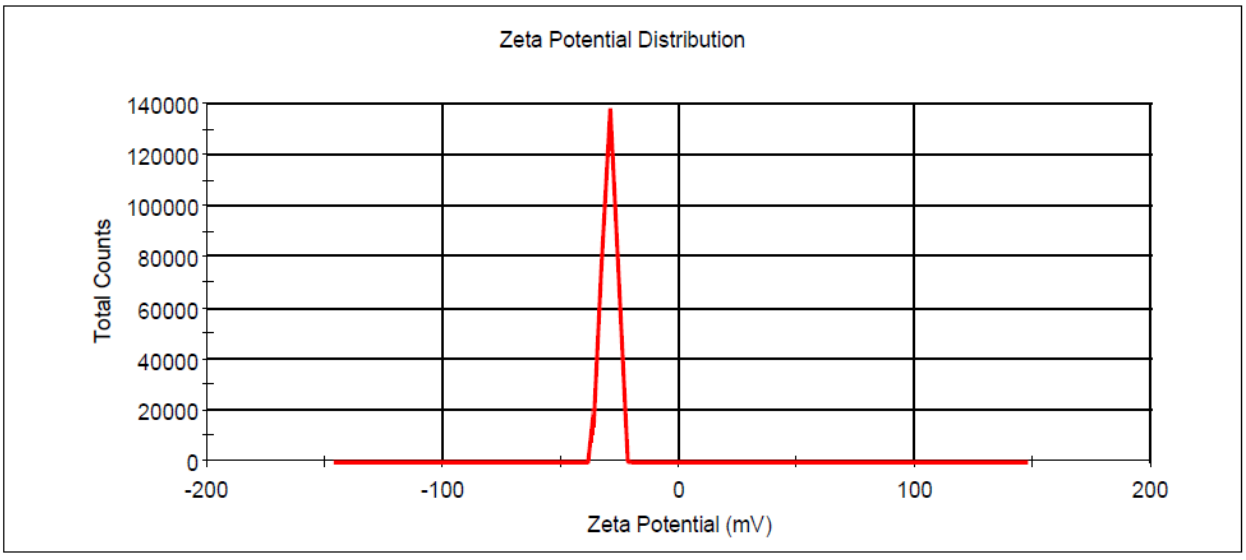

Figure 4. Zeta potential of formulation

Characterization of optimized formulation

1. Droplet size and PDI

Mean droplet sizes and PDI of the optimized nanoemulsion was 68.30 ± 2.32 nm and 0.167 ± 0.055, respectively (**Figure 3**). Optimized nanoemulsion had low PDI size thus showed the narrow size distribution.

2. Surface charge determination

Zeta potential values of optimized formulation was found to be -28.50 ± 0.12 mV (**Figure 4**). The obtained results suggesting more stable formulation.

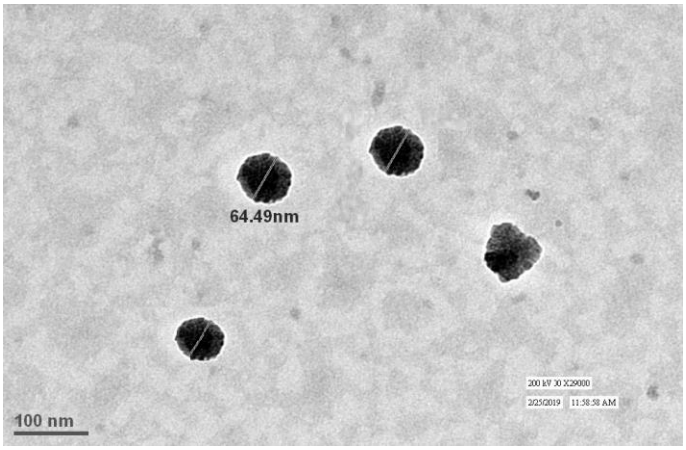

Figure 5. Transmission electron microscopy of formulation

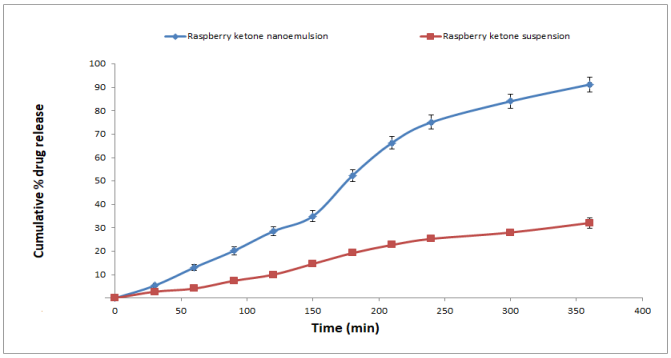

Figure 6. Comparative *in-vitro* release profile of raspberry ketone nanoemulsion and suspension

3. Refractive index and viscosity

Refractive index of optimized formulation was found to be 1.40 ± 0.01, showing isotropic nature of formulation. Viscosity of formulation was found to be 32.12 ± 1.40 cP, which is less than 50 cP hence confirming better tolerance on oral administration [17].

4. Surface morphology study

TEM images were taken of the optimized nanoemulsion (**Figure 5**). No aggregation was observed.

5. pH

pH of nanoemulsion was found to be 5.8 ± 0.3. The pH of formulation was within acceptable range for oral administration.

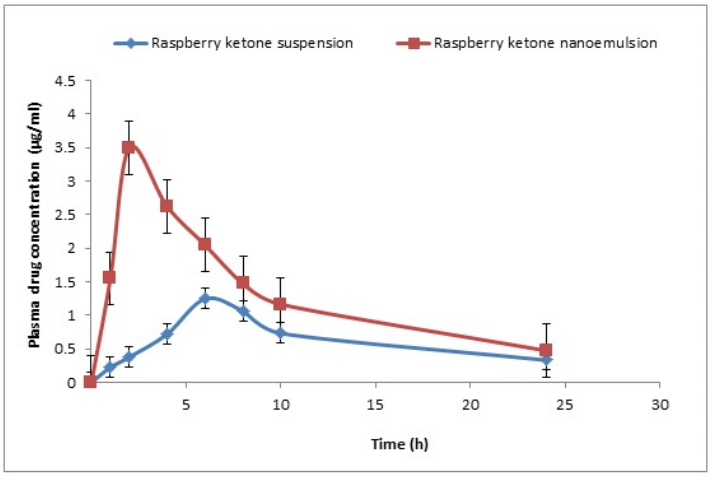

Figure 7. Comparative in vivo absorption profile for drug nanoemulsion and suspension

6. Percentage transmittance

Transmittance of nanoemulsion was found to be 99.50 ± 0.06 % showing that it was transparent and clear [13].

***In vitro* release studies using dialysis membrane**

In vitro release study results demonstrated that raspberry ketone showed faster release. It was due to solubilisation of raspberry ketone in the oil phase because of S_{mix}. It was found that raspberry ketone nanoemulsion showed 91.22 ± 3.21 % release in comparison to 32.11 ± 2.17 % released by suspension in 6 h (**Figure 6**).

Pharmacokinetic studies

The plasma profile of formulations were determined (**Figure 7**). Various pharmacokinetic parameters are listed in **Table 4**. The AUC $_{(0-24)}$ for nanoemulsion formulation (32.692 ± 2.621µg.h/ml) was significantly higher ($p < 0.05$) than raspberry ketone suspension (14.606 ± 1.516 µg.h/ml). The C_{max} of raspberry ketone nanoemulsion and raspberry ketone suspension was found to be 3.501 ± 0.086 and 1.247 ± 0.067µg/ml respectively. The value of AUC and C_{max} of nanoemulsion after oral administration were 2.2 fold and 2.8-fold higher than those of suspension, respectively.

CONCLUSION

Raspberry ketone loaded nanoemulsion was prepared. The formulation was developed by high energy emulsification technique in order to enhance its oral bioavailability. Raspberry ketone loaded nanoemulsion formulation showed significant improvement in *in vitro* release as compared to raspberry ketone suspension. The *in-vivo* study in Wistar albino rats gave significantly higher AUC and C_{max}. The value of AUC and C_{max} of nanoemulsion after oral administration were 2.2 fold and 2.8-fold higher than those of suspension, respectively.

ACKNOWLEDGEMENT

The authors are thankful for research facilities provided by School of Pharmaceutical Sciences, MVN University, Palwal, Haryana, India.

CONFLICTS OF INTEREST

The authors report no conflicts of interest.

DATA AVAILABILITY

N/A

FUNDING SOURCE

Self-financed

REFERENCES

[1] Lu, M., Guo, F., Fan, B., Ren, Z., Li, Q. Solubility and solution thermodynamics of Raspberry Ketone in pure organic solvents and binary solvent mixtures from T=(293.15 to 333.15) K. J. of Mol. Liq., 2017; 246: 332-41.

[2] Ewing, A.V., Wray, P.S., Clarke, G.S., Kazarian, S.G. Evaluating drug delivery with salt formation: Drug disproportionation studied in situ by ATR-FTIR imaging and Raman mapping. J. Pharm. Biomed. Anal., 2015; 10(111): 248–56.

[3] Filippa, M.A., Gasull, E.I.. Ibuprofen solubility in pure organic solvents and aqueous mixtures of cosolvents: Interactions and thermodynamic parameters relating to the solvation process. Fluid Phase Equilibria., 2013; 354: 185–90.

[4] Chen, X., Fadda, H.M., Aburub, A., Mishra, D., Pinal, R. Cosolvency approach for assessing the solubility of drugs in poly(vinylpyrrolidone). Int. J of Pharm., 2015; 494(1) :346–56.

[5] Xu, J., Luo, K.Q.. Enhancing the solubility and bioavailability of isoflavone by particle size reduction using a supercritical carbon dioxide-based precipitation process. Chem. Eng. Res.and Design. 2014; 92(11) :2542–9.

[6] Chen, Y., et al., Optimized mixed oils remarkably reduce the amount of surfactants in microemulsions without affecting oral bioavailability of ibuprofen by simultaneously enlarging microemulsion areas and enhancing drug solubility. Int. J. of Pharm., 2015; 487(1-2): 17-24.

[7] Qureshi, M.J., Mallikarjun, C., Kian, W.G. Enhancement of solubility and therapeutic potential of poorly soluble lovastatin by SMEDDS formulation adsorbed on directly compressed spray dried magnesium aluminometasilicate liquid loadable tablets: A study in diet induced hyperlipidemic rabbits. Asian J. Pharm. Sci., 2015; 10(1): 40-56.

[8] Poon, S.F., et al. Novel approach to pro-drugs of lactones: water soluble imidate and ortho-ester derivatives of a furanone-based COX-2 selective inhibitor. Bioorg. Med. Chem. Lett., 2005; 15(9): 2259-63.

[9] He, Y., Ho, C. Amorphous Solid Dispersions: Utilization and Challenges in Drug Discovery and Development. J. Pharm. Sci., 2015; 104(10): 3237–58.

[10] Mohanachandran, P.S., Sindhumol, P.G., Kiran, T.S. Enhancement of Solubility and Dissolution Rate: An Overview. Int. J. of Com. Pharm., 2010; 1(4):1–10.

[11] Kohli, K., Chopra, S., Dhar, D., Arora, S., Khar, R.K.. Self-emulsifying drug delivery systems: an approach to enhance oral bioavailability. Drug Discov. Today., 2010; 15(21-22): 958–65.

[12] Date, A.A., Desai, N., Dixit, R., Nagarsenker, M. Self-nanoemulsifying drug delivery systems : formulation insights , applications and advances. Nanomedicine., 2010; 5(10): 1595– 616.

[13] Kumar, S., Ali, J., Baboota, S. Design Expert® supported optimization and predictive analysis of selegiline nanoemulsion via the olfactory region with enhanced behavioural performance in Parkinson's disease. Nanotechnology., 2016; 27: 435101.

[14] Mohamed, H.E. et al. Raspberry ketone preserved cholinergic activity and antioxidant defense in obesity induced Alzheimer disease in rats. Biomed. and Pharmaco., 2018 ;107:1166-74.

[15] Attia, R.T., Abdel-Mottaleb, Y., Abdallah, D.M., El-Abhar, H.S., El-Maraghy, N.N. Raspberry ketone and Garcinia Cambogia rebalanced disrupted insulin resistance and leptin signaling in rats fed high fat fructose diet. Biomed and Pharmaco., 2019; 110: 500–509.

[16] Häkkinen, S.T., Seppänen-Laakso, T., Oksman-Caldentey, K.M., Rischer, H. Bioconversion to Raspberry Ketone is Achieved by Several Non-related Plant Cell Cultures. Front. Plant Sci., 2015; 6: 1035.

[17] Gupta, B.K., Kumar, S., Kaur, H., Ali, J., Baboota, S. Attenuation of oxidative damage by Coenzyme Q_{10} loaded nanoemulsion via oral route for the management of Parkinson's disease. Renjuvention Res., 2018; 21(3): 232-48.

Indo Global Journal of Pharmaceutical Sciences(ISSN 2249 1023; CODEN- IGJPAI; NLM ID: 101610675) indexed and abstracted in CrossRef (DOI Enabling), CNKI, UGC CARE Journal List, EMBASE (Elsevier), National Library of Medicine (NLM) Catalog (NCBI), ResearchGate, Publons (Clarivate Analytics), CAS (ACS), Index Copernicus, Google Scholar and many more. For further details, visit http://iglobaljournal.com