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Construction of Pseudoternary Phase Diagram and its Evaluation: Development of Self-dispersible Oral Formulation

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Abstract

The purpose of this study is to give an insight into the significance of pseudoternary phase diagram construction and its evaluation, as an important tool for the development of lipid based self-dispersible oral formulation. This formulation was designed in order to improve the oral efficacy of hydrophobic drug, which display dissolution rate limited absorption. Construction of pseudo-ternary phase diagram is an important tool for screening of self-dispersible formulation components and to assess the effect of different component on *in-vitro* performance of formulation. Spontaneity of formulation to convert into nano drug carrier and robustness to dilution inside gastrointestinal lumen is an important aspect of such lipid based formulation to predict its *in-vivo* performance. Thus our study provides an important tool for designing of lipid based formulation for improved oral delivery of low bioavailable drug.

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INTRODUCTION

The oral drug delivery is the most fascinating route for chronic drug therapy but it is dependent upon the bioavailability of the active form of the drug. Most of

the drugs are hydrophobic in nature and exhibit low oral bioavailability because of their poor solubility in gastrointestinal lumen (GI) [1,2]. Nowadays, lipid-based formulations are the most popular approach to increase the oral efficacy of hydrophobic drugs by incorporating into inert lipid vehicle and surfactant [3,4]. A self-dispersible oral formulation was developed using hydrophobic drug. Such formulations readily disperse as nanosized oil droplets under conditions of gentle agitation and digestive motility that would be encountered in GI lumen and influence absorption of drug by providing enormous interfacial areas with additional intestinal lymphatic uptake [5,6].

Construction of pseudoternary phase diagram is a critical step for the development of such lipid-based formulation, which self-disperses as thermodynamically stable nano drug carrier in GI lumen. It will provide the information of phase behavior between different formulation components. Since the free energy required to form nanosized oil droplets is very low, therefore developed formulation would be thermodynamically spontaneous [7]. The ease of self-emulsification is to be related to the ease of water penetration into surfactant formed layer around the surface of oil droplet [8]. This will also provide a mechanical barrier to coalescence. It was constructed to optimize the ratio of different formulation components in such a way that it had efficient self-emulsification potential, optically isotropic and thermodynamically stable. The aim of this study was to develop a simple method to identify the components of self-dispersing lipid formulation by constructing the pseudo-ternary phase diagram and optimize the ratio of different components on the basis of phase behavior study.

MATERIALS AND METHODS

Materials

Propylene glycol monocaprylate was gifted by Nikko Chemicals (Tokyo, Japan), Caprylo caproyl macrogol-8-glyceride, Polyglyceryl-6-dioleate, Transcutol HP and Glycerol monooleate were provided by Gattefosse (Saint Priest, Cedex France). Polyoxyethylene (20) sorbitan monolaurate, Polyoxyethylene (20) sorbitan monooleate, Polyethylene glycol 300 and other chemicals were purchased from Merck (Schuchardh, Hokenbrunn, Germany).

Methods

Screening of component

Different components of formulation for construction of pseudoternary phase diagram like oil phase, surfactant and co-surfactants were screened. Different oil phases were screened on the basis of maximum drug solubility. It is very important in the case of oral formulation development because contribution of other components in solubilization of target dose of drug could have lead to a risk of drug precipitation in GI lumen due to lowering of solvent capacity [3,9]. Different surfactants were screened on the basis of their maximum emulsifying ability for selected oil phase. Different co-surfactants were screened by determining the maximum nanoemulsifying area obtained in developed phase diagram for selected oil phase and surfactants.

Determination of emulsification efficiency

To find an appropriate surfactant for oil phase having maximum drug solubility, 5 µL of oil was added with vigorous vortexing in 10% surfactant aqueous solution to form a single phase isotropic system. The addition of the oil was repeated until the solution became turbid. The transparent samples of surfactants solution containing maximum amount of emulsified oil were allowed to equilibrate for a minimum of 24 h and then examined visually for single phase isotropic system.

Construction of phase diagram

The phase diagrams of ternary systems (oil phase, surfactant phase and aqueous phase) were constructed using aqueous titration or spontaneous

emulsification method. Optimized surfactant was dissolved in oil phase in ratios of 9:1, 8:1, 7:1, 6:1, 5:1, 4:1, 3:1, 2:1, 1.5:1, 1:1, 0.66:1, 0.43:1 & 0.25:1 in glass vials at room temperature. Each ratio of surfactant and oil phase was then titrated drop by drop continuously with distilled water using micropipette by vortex mixing till it turned turbid. The phase behavior of each ternary system during titration was observed minutely. The percentage composition of the component in each ternary system was determined and the observed results were plotted on triangular co-ordinates to construct the phase diagrams.

Optimization of co-surfactants

Co-surfactants were added to obtain nanoemulsion systems at low surfactant concentration, which further reduced the interfacial tension and increased the fluidity of the interface [10,11]. For optimization, different co-surfactants like Polyethylene glycol 300, Propylene glycol, Polyglyceryl-6-oleate and Transcutol HP were completely solublized as single system in selected surfactant at a fixed ratio of 1:1. The efficiency of this different type of Smix on nanoemulsification was assessed by constructing phase diagram using titration method. The different types of Smix were mixed in oil phase in ratios as 9:1, 8:1, 7:1, 6:1, 5:1, 4:1, 3:1, 2:1, 1.5:1 & 1:1 in glass vials and then titrated continuously.

Self-emulsification performance

The spontaneity of self-emulsification of formulation optimized from nanoemulsification region of phase diagram was assessed using a standard USP II dissolution apparatus by determining rate of emulsification [12]. Each formulation was added to 200 mL of 0.1N HCl or purified water at 37+0.5 °C. A standard stainless steel dissolution paddle rotating at 50 rpm provided gentle agitation.

Robustness to dilution in GI lumen

The *in-vitro* performance of the formulations optimized from nanoemulsification region of phase diagram was assessed for the robustness to GI lumen dilution by determining percent transmittance of 100 times diluted formulation at 640 nm using double distilled water as blank in UV spectroscopy [13].

RESULTS AND DISCUSSION

Screening of components

Different formulation components were screened to conclude that all the excipients should be pharmaceutically acceptable for oral delivery and come under GRAS (generally regarded as safe) category. In case of oral formulation development, solubility of the therapeutic dose of drug in the acceptable volume of oil phase is an important factor for its selection. Different classes of oil like Ethyl oleate, Isopropyl myristate, Propylene glycol monocaprylate (HLB = 6), Propylene glycol dicaprylocaprate (HLB = 2), Propylene glycol laurate (HLB = 4), Glyceryl monolinoleate (HLB = 4), Glyceryl monooleate (HLB = 3) were screened for drug solubility. Among all these, drug solubility was found maximum in Propylene glycol monocaprylate and therefore it was selected as oil phase.

Determination of emulsification efficiency

To form oil in water nanoemulsion, the required HLB value of surfactant should be greater than 10 (KOMORRU). Four types of non-ionic surfactants were screened having HLB value greater than 10 and physically compatible with selected oil phase. It included Caprylocaproyl polyoxyl-8-glycerides (HLB = 14), Polyoxyethylene (20) sorbitan monolaurate (HLB = 16.7), Polyoxyethylene (20) sorbitan monooleate (HLB = 15) and Polyoxyl-15-hydroxystearate (HLB = 15). Amongst these, polyoxyethylene (20) sorbitan monolaurate had maximum emulsifying efficiency for selected oil phase.

Construction of phase diagram

Ternary phase diagram was constructed by selecting Propylene glycol monocaprylate as oil phase, Polyoxyethylene (20) sorbitan monolaurate as surfactant and water as aqueous phase. It was constructed by performing aqueous titration according to table 1. In ternary phase diagram large liquid crystals (LC) region was obtained as compared to small nanoemulsification region. Liquid crystalline area was obtained with high surfactant/oil ratio towards the bottom of phase diagram near surfactant rich apex. When surfactant/oil ratio was less than 1, two phase system was observed towards oil rich apex. There was small nanoemulsification region i.e. single phase isotropic system observed towards aqueous rich apex, when surfactant/oil ratio was more than 1 as shown in figures 1.

Table 1: Titration chart used in the construction of pseudo-ternary phase diagram

Oil µL	Surfactant (or Smix) µL	Water µL	Water added µL	Total µl	Oil %	Surfactant (or Smix) %	Water %
20	100	14	14	134	14.93	74.63	10.45
20	100	22	8	142	14.08	70.42	15.49
20	100	30	8	150	13.33	66.67	20.00
20	100	40	10	160	12.50	62.50	25.00
20	100	53	13	173	11.56	57.80	30.64
20	100	65	12	185	10.81	54.05	35.14
20	100	80	15	200	10.00	50.00	40.00
20	100	100	20	220	9.09	45.45	45.45
20	100	120	20	240	8.33	41.67	50.00
20	100	147	27	267	7.49	37.45	55.06
20	100	180	33	300	6.67	33.33	60.00
20	100	225	45	345	5.80	28.99	65.22
20	100	280	55	400	5.00	25.00	70.00
20	100	360	80	480	4.17	20.83	75.00
20	100	480	120	600	3.33	16.67	80.00
20	100	680	200	800	2.50	12.50	85.00
20	100	1100	420	1220	1.64	8.20	90.16
20	100	2300	1200	2420	0.83	4.13	95.04

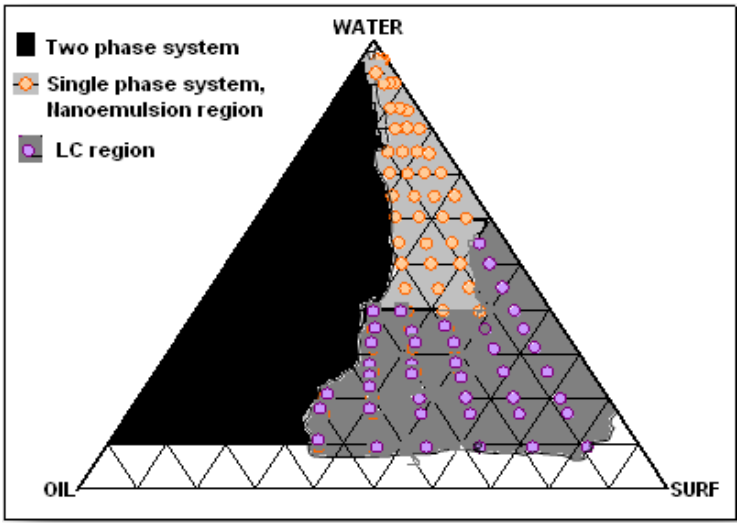

Figure 1: Pseudoternary phase digram for phase behavior study

Optimization of co-surfactants

Large amount of surfactants may cause gastrointestinal irritation after oral administration, therefore co-surfactants was added in the formulation to reduce its concentration. Co-surfactants also lead to greater penetration of the oil phase in the hydrophobic region of the surfactant monomers by increasing the mobility of the hydrocarbon tail thereby further decreasing the interfacial tension, which leads to increase in the entropy of the system [5,14]. This all will result in improvement of the self-emulsification performance. Nanoemulsifying area in phase diagram was used as the assessment criteria for the screening of co-surfactants. Larger the nanoemulsion region, greater will be the nanoemulsification efficiency of the system. When Polyglyceryl-6-oleate was added along with Polyoxyethylene (20) sorbitan monolaurate in equal ratio (1:1), a large LC region with very limited nanoemulsion area was obtained. This may occurred due to very viscous nature of Polyglyceryl-6-oleate and low HLB (=10) value as compared to generally used co-surfactants in self-emulsifying formulation. After that propylene glycol, polyethylene glycol 300 was assessed separately along with Polyoxyethylene (20) sorbitan monolaurate in equal ratio (1:1). The region which was LC in 1:0 ternary systems changed to easily flowable but small nanoemulsion region. Now Transcutol HP was added along with Polyoxyethylene (20) sorbitan monolaurate in equal ratio (1:1). The whole area which was LC in 1:0 ternary systems changed to easily flowable nanoemulsion area. Besides this, surfactant - cosurfactant mass ratio had been found to be also a key factor in influencing the phase properties i.e., size and position of nanoemulsion region [15]. The type and concentration of oil employed also play an important role [16]. Thus Transcutol HP gave the maximum nanoemulsion region as compared to the other tested cosurfactants. This may be attributed to the fact that the addition of Transcutol HP being a cosurfactant may lead to greater penetration of the oil phase in the hydrophobic region of the surfactant monomers. Thus the presence of co-surfactant and its type affected the phase behavior of the nanoemulsion. It was also observed that decrease in the oil level lead to an increase in the area of nanoemulsion formation. This fact suggested that the oil constitutes the inner phase of the nanoemulsion droplets, which is consistent with a direct o/w type structure [17].

Self-emulsification performance

The spontaneity of self-emulsification of formulation optimized from nanoemulsification region of phase diagram was done using a standard USP II dissolution apparatus. It was found that all selected formulation spontaneously emulsified into nanoemulsion as drug carrier within 2 minutes. This involves the erosion of a fine cloud of small globules from the monolayer around emulsion droplets [18]. It was observed that self-emulsification time of formulation having surfactant/ co-surfactant ratio less than 1 is low in comparision to formulation having surfactant/ co-surfactant ratio greater than 1. This might be due to high viscosity imparted by Polyoxyethylene (20) sorbitan monolaurate and increase in the free surface energy of system thereby increase in the self-emulsification time.

Robustness to dilution in GI lumen

Developed formulations spontaneously dispersed in GI lumen to form fine emulsion as nano drug carrier with enormous interfacial areas for improved drug absorption of selected hydrophobic drug. Therefore, it is important that formed nanoemulsion should be robust to infinite dilution in the GI lumen and does not undergo drug precipitation due to phase separation or other GI factor. To assess such condition, optimized formulation from phase diagram was evaluated for dispersability study by diluting 100 times in 0.1 N HCl and distilled water. Percent transmittance of diluted formulation was determined by UV-spectroscopy at 640 nm. It was

found that formulation with surfactant/ co-surfactant ratio more than 1 has percent transmittance closer to 100%. It indicates that globule formed after self-emulsification will be in nano dimension because globules of nano size range avoid the scattering of light, and most of the incidents light on sample solution get transmitted. The globule size formed after the self-emulsification is very important because it will affect the rate and extent of drug release as well as drug absorption [19,20]. It was also observed that the formulations optimized from phase diagrams in which the nanoemulsifying area extended towards an aqueous-rich apex could be diluted to a larger extent and having percentage transmittance closer to 100%. Thus, it could be concluded that formulations selected from phase diagram with surfactant/ co-surfactant ratio greater than 1 is optimum for development of self-dispersible oral formulation because high surfactant concentration decreases the thermodynamic activity and increases the affinity of the drug towards the vehicle [21]. Therefore, the amount of different formulation components should be optimized so judiciously that it does not affect the *in-vivo* performance of developing formulation.

CONCLUSION

Proper selection of components and its amount is very important factor for development of a robust self-dispersible lipid formulation for oral delivery. Construction of pseudo-ternary phase diagram is an important tool to assess the effect of different formulation component on *in-vitro* performance. It provides scientific basis for the selection of different components and *in-vitro* performance of optimized formulation can be correlated with its *in-vivo* efficacy.

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