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STUDY OF DIFFERENT EXCIPIENTS SUCH AS SOLID LIPID, LIQUID LIPID, SURFACTANT FOR THE DEVELOPMENT OF QF LOADED NLC.

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Abstract

Solubility and dissolution of a poor water-soluble drug are the two major barriers for formulation scientists in development of drug delivery. Many of the potent drugs do not show the therapeutic effects due to solubility issues but may show toxicity issues when used in high doses. Solid dispersion (SD) technology is an excellent tool for enhancing the solubility and dissolution and hence related bioavailability. NLC formulation is a potential way for enhancing the bioavailability of lipophilic drugs with solubility and first pass metabolism problem. Formulation of NLCs requires few ingredients *viz.* solid lipid, liquid lipids, surface active agent and water. The NLC is a smarter drug delivery system with unique advantages such as higher drug loading; higher entrapment of drug, sustained drug release behavior and eventually enhanced drug absorption as compared with other lipid-based drugdelivery system and feasibility of large-scale production makes NLC as versatile delivery system.In present study, QF loaded NLCs was prepared using hot homogenization followed by the ultrasonication method. NLCs batch F3 (0.1% of QF, 0.7% of GMS,0.4% of capmul MCM EP, 1.5% poloxamer 188, 0.6% egg lecithin and water up to100%) showed excellent stability specified by ZP, high % EE value, drug loading capacity with sustained action. The drug release patterns from the QF-NLCs displayed a biphasic drug release behavior with burst release at the initial stage followed by sustained release. Thus, NLCs seems to be reasonable delivery systems for oral administration of QF and may be used as alternate strategy to achieve ameliorated release and prolonged action of QF. In future, QF loaded NLCs may be used inclinical subjects for achieving better outcomes.

KEYWORDS: Central composite design; Nanostructured lipid carriers; Poloxamer 188; Quetiapine Fumarate; Response surface methodology.

INTRODUCTION

LDC system contains drug linked to lipid particles enhances drug loading up to 33%. However, LDC

suffered with few demerits such as particle size growth, uncertain gelation tendency, sudden polymeric transitions and low drug loading (Olbrich et al., 2004 and Das et al., 2013). In order to address LDC disadvantages, SLN system was developed in year 1991 and an effective alternate drug delivery system (Radtke et al., 2005). SLN can be characterized as small lipid containing preparations which are biocompatible and biodegradable systems with large surface area and (Cavalli et al., 1993 and Sarangi et al., 2016). Even more, SLN strategy has been successfully applied for oral administration of cyclosporine and paclitaxel in effective therapy of cancer (Radtke et al., 2005).

The second-generation lipid carrier is usually composed of solid lipids and liquid lipids together in a system. This mixing causes depression in melting point of substrates and converts the mixture into solid form at body temperature and termed as NLC. NLC shows a high drug loading characteristic with minimum drug expulsion as compared to SLN. Solid lipids like glyceryl behenate, glyceryl palmitostearate, glyceryl monostearate and stearic acid are mostly used in the formulation of NLC. MCT and oleic acid are frequently used liquid lipids used in the formulation of NLC. The liquid lipid proportion in the lipid blend also modifies the quality and characteristics of NLC.

MATERIALS AND METHODS

Selection of solid lipids

The solid lipid used in present work contains mixture of various chemical compounds with high M.P. (higher than 40ºC). After exhaustive literature survey, some biodegradable solid lipid and liquid lipid and emulsifier from different categories were selected *viz.* hard fats (stearic acid), triglycerides (monegyl- T18, monegyl-D207), partial glycerides (glyceryl monostearate).In case of solid lipids, 25 mg of QF was transferred to a glass beaker. Weighed quantity (0.05gm) of various solid lipid was taken, added in small increments in the beaker containing QF and the mixture was heated using temperature regulated water bath at the 10°C above the M.P. of respective solid lipid. The addition of solid lipid was continued until a clear melt was obtained. Obtained melt was spread on hot glass slide using hot spatula and observed microscopically to confirm formation of clear lipid mixture (Shah et al., 2016; Sansare et al., 2019).

Selection of liquid lipid

Quantity of liquid lipid (oil) plays important part in governing PS and release rate of drug. It reduces viscosity and surface tension and help in producing small sized NLC and higher molecular mobility (Tiwari et al., 2011 and Chen et al., 2010). Addition of liquid lipid to solid lipid causes decrease in PS due to reduction in viscosity (Chen et al., 2010). Liquid lipid causes enhancement of % EE and solubility of API (Tran et al., 2014).Oil was selected depending on the solubility of the QF in oil. Different oils were selected for the present study namely capmul MCM EP, oleic acid, isopropyl myristate, castor oil and

olive oil. Excess of QF was placed in vials that containing 5 g of oil and resulting mixture was vortexed for 10 min. Further, vials with stopper were placed in an orbital shaking incubator (Dolphin) at 25± 2.0°C for 48 hours to attain equilibrium. After this, samples were centrifuged (R2, REMI) at 10,000 rpm for 10 min. The quantity of QF in oils was determined by removing supernatant from each vial. The concentration of QF in each sample was analyzed by UV at 244 nm, after diluting samples with methanol (Talele et al., 2018, Shah NV et al., 2016, Shah B et

Optimization of ratios of solid lipid to liquid lipid

The mixture comprising of both lipids were prepared homogenous. To optimize the ratio of lipid, miscibility test between the selected lipids namely GMS and capmul MCM EP was performed. The selected solid lipids and oil were weighed in the different % ratios (60:40, 70:30, 63.636: 36.363) in glass vials. This blend was heated to a temperature 10°C above the M.P. of the solid lipid. Thereafter, the liquid blend vortexed and smeared on glass slide. Upon solidification, a dry filter paper was pressed on this lipid blend and observed for sign of oil drops, if any. The mixture that does not showed any oil drop on filter paper was considered as miscible and was selected for the development of QF loaded NLCs (Sansare et al., 2019).

RESULTS AND DISCUSSION

Selection of solid lipid

Results of solubility analysis revealed that QF exhibits less solubility in monegyl- D207, monegyl T 18 and stearic acid than solubility in glyceryl monostearate (GMS) (Table 13). QF crystals were completely dissolved in GMS and hence GMS was selected as solid lipid. It is noticeable that GMS is having GRAS status and is biodegradable in nature at in vivo.

Table 13: Result of selection of solid lipid

S,No.	**Solid lipid type**	**Solid lipid**	**Observation**
1	Hard fats	Stearic acid	No clear melt
2	Triglycerides	Monegyl- T18 (Glycerol Tri Stearate)	No clear melt
3	Triglycerides	Monegyl- D207 (Glycerol Di Stearate)	No clear melt
4	Partial glycerides	Glyceryl monostearate	Clear melt

Selection of liquid lipid

Results of study indicated that QF possesses maximum solubility (23.42±0.97 mg/ml)

in capmul MCM EP has maximum drug solubility when compared to oleic acid,

isopropyl myristate, castor oil, labrafac lipophile WL 1349, olive oil (Table 14 and

Figure 15). Notably, capmul MCM EP has been known to increase the bioavailability of drugs. Therefore, it was selected as liquid lipid with GMS in the preparation of NLC (Lawrence et al., 2000, Shah B et al., 2016).

Table 14: Solubility of QF in different liquid lipid at 25°C

Sr. No.	Liquid lipid	Solubility (mg/ml	
1	Capmul MCM EP	23.32±0.97	
2	Oleic acid	17.21±0.50	
3	Isopropyl myristate	22.30±0.90	
4	Castor oil	10.17±0.58	
5	Labrafac lipophile WL 1349	12.70±0.47	
6	Olive oil	14.22±0.53	

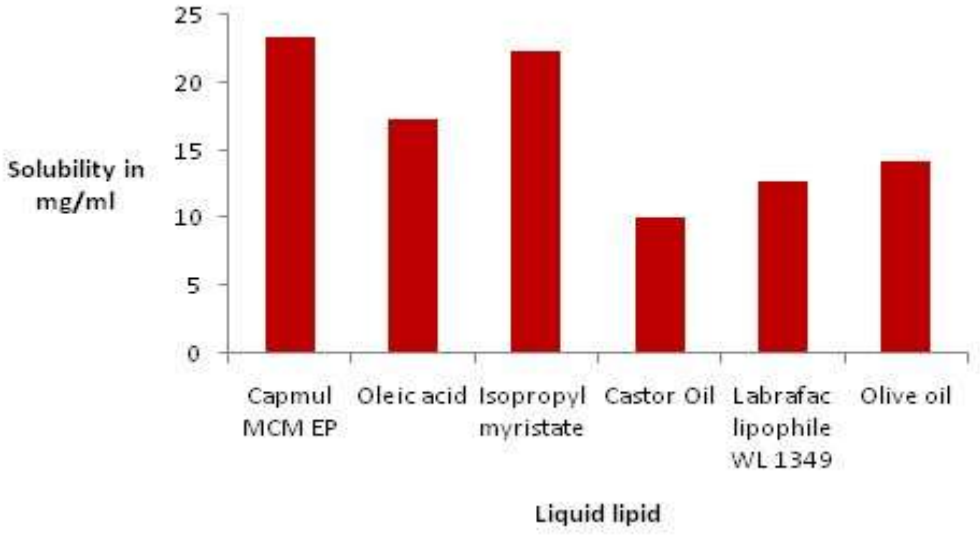

Figure 15: Solubility of QF in different liquid lipid at 25°C Optimization of ratios of solid lipid to liquid lipid

After solidification of selected solid lipid and liquid lipid in different % ratios (60:40, 70:30, 63.636: 36.363), they were applied to dry piece of filter paper and the sample which did not show any oil droplets on the surface of filter paper was considered miscible was selected for use in the development of trial batches of QF loaded NLCs.

Conclusion

In present study, QF loaded NLCs was prepared using hot homogenization followed by the ultrasonication method. NLCs batch F3 (0.1% of QF, 0.7% of GMS,

0.4% of capmul MCM EP, 1.5% poloxamer 188, 0.6% egg lecithin and water up to 100%) showed excellent stability specified by ZP, high % EE value, drug loading capacity with sustained action. The drug release patterns from the QF-NLCs displayed a biphasic drug release behavior with burst release at the initial stage followed by sustained release. Thus, NLCs seems to be reasonable delivery systems for oral administration of QF and may be used as alternate strategy to achieve ameliorated release and prolonged action of QF. In future, QF loaded NLCs may be used in clinical subjects for achieving better outcomes.

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CONFLICT OF INTEREST::

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

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