P-003 **Fabrication of of binary lipid matrix based solid lipid nanoparticles for oral delivery of repaglinide**

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INTRODUCTION AND OBJECTIVES

The aim of this work was to develop prolonged release binary lipid matrix based solid lipid Nanoparticles (SLNs) of repaglinide (RG) for oral intestinal delivery and to improve the bioavailability of RG. Binary lipid nanoparticles were designed by using glycerol monostearate (GM) and tristearin (TS) as lipid core materials and Pluronic-F68 as stabilizer. Single lipid matrixes have perfect crystal lattice which is responsible for drug expulsion and consequently for less EE and physical instability (Muller 1995and Porter 2001).On other side, binary lipid matrix can creates deformation in crystal order of lipids and avoid the drug expulsion. So as to improve the EE and physical stability of SLNs, an attempt was completed to disturb the crystal lattice (crystal order) of the monoglyceride by the addition of titrated amount of triglyceride.

MATERIALS AND METHODS

The SLNs were prepared by use of modified solvent injection method (Schubert 2003). The basic principle for the formation of SLNs by modified solvent injection method is lipid precipitation in which the lipids (GM, TS and lecithin) along with RG are dissolved in an organic solvent and rapidly injected into an aqueous phase containing the surfactant (Pluronic-F68) under continuous mechanical stirring. RG loaded SLNs obtained using GM and in combination with partial amount of TS (binary lipid matrix), were abbreviated as RGM (GM:TS :: 100:0), $RGMT_{10}$ (GM:TS :: 90:10), $RGMT_{20}$ (GM:TS :: 80:20) and $RGMT_{30}$ (GM:TS :: 70:30), respectively.

The prepared SLNs were characterized for their particle size, polydispersity index (PDI), zeta potential, entrapment efficiency(EE), differential scanning calorimetric (DSC), *in vitro* drug release, particle surface studies (Transmission electron microscopy analysis with electron diffraction pattern) and physical stability at 30°C /65% RH for 3 months.

RESULTS AND DISCUSSION

Nanoparticle sizes and PDI were ranged from 149±2.20 to 327±2.30 nm and 0.169 ±0.019 to 0.290 ±0.042, respectively for all the batches, which shows the narrow particle size distribution. The smallest particle sizes were found in batch $RGMT_{30}$ (70:30) and the largest particles were seen in batches RGM (100:0) > $RGMT_{10}$ > (90:10) > $RGMT_{20}$ (80:20). The zeta potential of the studied formulations varied from -23.21 ±2.30 to -24.87 ±2.41 mV which is nearer to -25 mV of ideal stabilization (Singh 2007).

In all prepared batches total drug content (assay) was nearer to 98%. The EE of the RG-SLNs were in the order of RGM (60.10±1.98) < $RGMT_{10}$ (66.20 ±1.85) < $RGMT_{20}$ (78.31 ±2.23) < $RGMT_{30}$ (88.35 ±2.50). The higher EE with the binary lipid matrix based SLNs ($RGMT_{30}$) is attributed to the deformation of the crystal lattice of the GM lipid by TS lipid. Complete RG release (100%) was achieved within 8 h from the control RG suspension across the dialysis bag which indicates rapid diffusion of the RG. In case of the control RG suspension the time required for 50% drug release ($T_{50\%}$) was 1.5 h whereas from SLNs were: RGM (2.34±0.052 h), $RGMT_{10}$ (3.19±0.103 h) , $RGMT_{20}$ (3.41±0.037 h) and $RGMT_{30}$ (4.15±0.03 h). The prolonged drug release was observed in $RGMT_{30}$ batches as compared to RGM (Fig. 1).

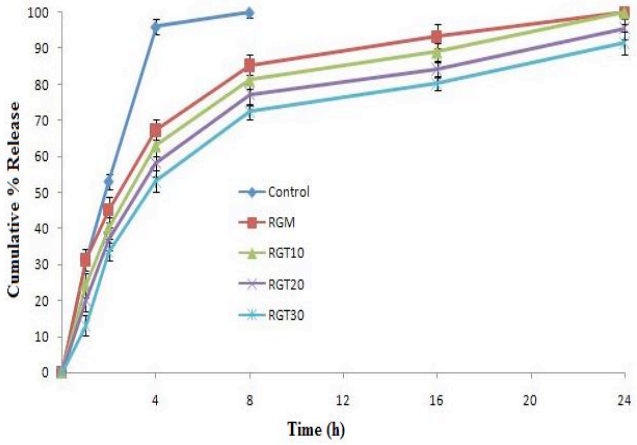

Fig. 1: In vitro release of repaglinide from repaglinide suspension and RG-SLNs batches

DSC gives an insight into the melting and recrystallisation behaviour of crystalline material like lipid nanoparticles (Bunjes 2001). DSC thermograms shows the massive crystal order disturbance (lattice defects) by using tristearin.The external morphological study using TEM revealed that placebo nanoparticles as well as drug loaded nanoparticles were spherical in shape (Fig. 2).

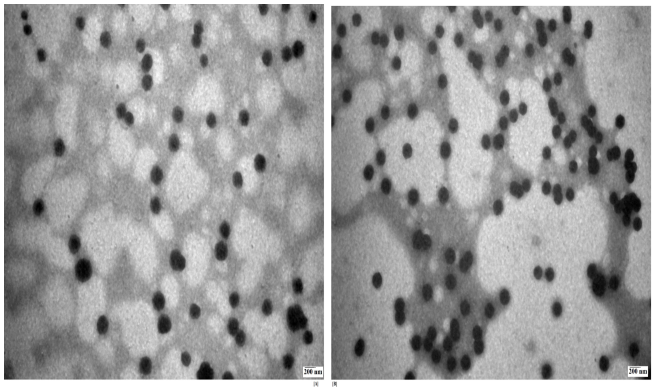

Fig. 2: Transmitted electron micrographs of Placebo SLN and $RGMT_{30}$

ED of the drug loaded (RGMT30) and placebo (without drug) nanoparticles in TEM revealed the crystalline state of the SLNs (Fig. 3A and 3B). These images clearly demonstrate that ring patterns in the electron diffraction were reduced in drug loaded nanoparticles owing to presence of amorphous RG (Muthu 2007). This study confirmed that RG was well incorporated into the core of lipid nanoparticles (Figure 3B).

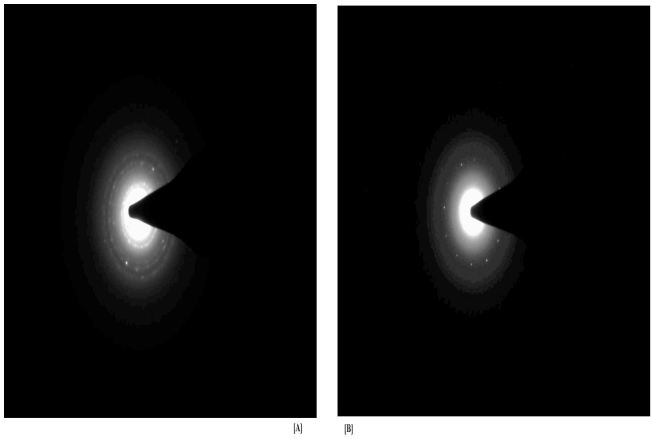

Fig. 3: Electron diffraction ring pattern for Placebo SLN and $RGMT_{30}$

The presence of amorphous RG was also revealed in DSC study. SLN prepared with tristearin (TS) showing insignificant changes in the evaluation parameters on storage at 30°C /65% RH for 3 months.

CONCLUSION

The present study confirms that the modified solvent injection is suitable technique for the preparation of RG nanoparticles. By using binary lipid matrix, the high EE was achieved as disrupt the perfect crystal lattice which is responsible for drug expulsion. DSC, TEM and ED ring pattern showed the amorphous state of RG in SLNs. The stability data and in vitro release profile indicated controlled release of the drug and excellent physical long-term stability in binary lipid based SLNs.

REFERENCES

- Muller et al. (1995). *Solid lipid nanoparticles (SLN)-an alternative colloidal carrier system for controlled drug delivery*. Eur. J. Pharm. Biopharm. 41, 62-69.
- Porter et al. (2001). *In vitro assessment of oral lipid based formulations*. Adv. Drug Deliv. Rev. 50, S127-S147.
- Schubert et al. (2003) . *Solvent injection as a new approach for manufacturing lipid nanoparticles: Evaluation of the method and process parameters*. Eur. J. Pharm. Biopharm. 55,125-131.
- Singh et al. (2007). *Preparation and characterization of nanoparticles containing an atypical antipsychotic agent*. Nanomed. 3, 305-319.
- Bunjes et al. (2001). *Crystallization tendency and polymorphic transitions in triglyceride nanoparticles*. J Microencapsul. 18,149-58.
- Muthu et al. (2008). *Studies on biodegradable polymeric nanoparticles of risperidone:In vitro and in vivo evaluation* . Nanomed. 2, 233-240.