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Research Article
Local Administration of Methylated Prednisolone Comprising Solid Lipid Nanoparticles Improves Post Traumatic Spinal Cord Injury

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Abstract

Background and Objective: Methylprednisolone (MP) inhibits secondary inflammations associated with spinal cord injury (SCI), however, its effectiveness is required to be improved because it shows higher protein binding if administered orally or intravenously. Therefore, this study aimed to develop solid lipid nanoparticles (MSLN) based semisolid hydrogel of MP to ensure maximum drug availability at the spinal cord injury site following local administration. **Methodology:** The MSLNs were prepared by pre-emulsification ultrasonic probe sonication method. The MSLN was characterized on the basis of entrapment efficiency, particle size, surface charge, polydispersity index and morphological characteristics. Further, Carbopol 940 gel of MSLN (MSLNG) was by pH sensitive gelling. The MSLNG was evaluated for *in vitro* release, *in vitro* cytotoxicity and *in vivo* potential against post SCI like conditions. **Results:** Shape of MSLN was spherical and surface was smooth. Droplets of size, zeta potential and polydispersity index were 76.7±7.8 nm, -26.7 mV and 0.231, respectively. Its entrapment efficiency was observed to be 48.9%. Viscosity and pH of the gel were 88205±47.72 cP and 4.68, respectively. The MSLN retained cells were more viable as compared with drug solution at the same dose. Release of the drug from MSLNG was observed to be controlled as compared to gel of drug solution (MPG). The MSLNG and MPG were able to reduce the level of cytokines such as Il-1β and TNF-α but only MSLNG showed significant change in the level of cytokines. Based on behavioral data assessment and histopathological investigations, MP delivery through MSLNG was found to be more effective in treating post SCI conditions when compared with MPG. Higher efficacy in the case of MSLNG could be due to the controlled release of MP at local site. **Conclusion:** Lipid based hydrogel of MSLNG was developed successfully which might offer safe and effective mean for the treatment of post SCI like conditions.

Key words: Spinal cord injury, solid lipid nanoparticles, Methylprednisolone, hydrogel, inflammation

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Spinal cord injury (SCI) is a trauma condition that may lead in a lifelong disability as it is produced after physical destruction of the neuronal cells and blood vessels of the spinal cord. This is followed by the initiation of secondary inflammation that jointly damages the tissues and exacerbates the lesions. These pathological events help to start an array of biochemical alterations that lead to apoptosis. Apoptosis of neuronal cell invites secondary events which cause distress to SCI. Today secondary events associated with SCI have become a challenge and therefore, an efficient neuro-protective component is needed. Primarily corticosteroids are used in such conditions however the most effective treatment option is still being searched[1]. Steroids face various limitations when administered through oral or intravenous route of drug administration[2]. One has to cross blood brain barrier, withstand inflammatory and acidic/basic environment and to avoid first pass metabolism to reach the injury site like post SCI[3]. Treatments available are not as effective as to manage such conditions. This could be due to the rapid metabolism, shorter elimination half-life, less oral bioavailability, slight aqueous solubility, less partition coefficient, high protein binding and many more[2].

One of such kind of pharmaceuticals is Methylprednisolone (MP) which is synthetic glucocorticoid (FDA approved) and widely used in the treatment of post SCI like inflammatory conditions[4]. Its anti-inflammatory effect is due to the involvement with lipocortins, which regulate the expression of prostaglandins and interleukin[5]. Effectiveness of oral Methylprednisolone is observed to be limited even its oral bioavailability is very high. This is due to the very high protein binding (about 78%). Most of the MP gets bind with the proteins present in flowing blood and does not get accumulated in sufficient quantity at SCI sites. This is considered as the main reason behind the lower efficacy of MP in the treatment of SCI. Higher protein binding in the systematic circulation and inadequate site specificity offer an opportunity to the researchers to improve its potency. At the therapeutic dose when administer via i.v., route, it sometime offers various side effects[4]. It is rather difficult to deliver MP with higher first pass metabolism via oral route (having aqueous environment) and high protein binding via intravenous route[6]. Improving pharmacokinetic parameters and neurovascular availability of MP could be the possible and suitable ways to enhance its efficacy[7]. This could be achieved by avoiding its exposure to the proteins after encapsulating it in a carrier which can improve its distribution even in the aqueous environment and administering it locally at SCI site[3, 7].

The most appropriate drug carrier could be lipid based solid nanoparticles (MSLN) that have potential to encapsulate the drug, sustain their release and improve its distribution[8]. Its nano size range meant to show rapid penetration however, lipidic membrane helps in efficient interaction with the biological environment.

Lipid forms a bilayer which interacts with biological membrane and if the size of formed particle is very less, particle interaction become very efficient. Several lipidic polymers such as pectin, lecithin which have been used as emulsifiers and wall forming materials[9]. Precirol ATO 5 belongs to the family hydroxyl fatty acid which is used as food additive. It usually presents in cell membrane and may interact with cell membrane. The miniature lipid particle was selected that might ensure control release of the encapsulated drug. Authors have hypothesized to develop hydrogel thickened, precirol ATO 5 stabilized lipid nanoparticles for local administration of MP at SCI site. The MSLN was expected to penetrate and interact with the biological membrane efficiently and release MP in a very controlled manner so as to avoid its instant or inadequate availability around there. This study aimed to discover solid lipid nanoparticles (MSLN) based semisolid hydrogel of MP to ensure maximum drug availability of this drug at the spinal cord injury site following local administration. This dosage form can be beneficial for safer and effective mean for the treatment of post SCI like conditions and will help the researcher to uncover the critical areas of the treatment of secondary inflammations associated with SCI like conditions that many researchers were not able to explore.

MATERIALS AND METHODS

All the experiments of formulation and development were performed in the Laboratory of Pharmaceutical Sciences and surgery of the animals was performed in Pharmacological Department of The Xiangya Hospital of Central-South University in 2016. Some study was carried out in Hunan Engineering Laboratory of Advanced Artificial Osteo-materials.

Materials: Materials used were purchased from China only. Methylprednisolone, Tween 20, chloral hydrate, dialysis membrane of 2 kDa MWCO and precirol ATO 5 were from Sigma Aldrich Chemie, Carbopol 940 (C940), hydroxyethyl cellulose (HEC), methyl paraben (MP), dimethyl sulfoxide

(DMSO), Span 80, propyl paraben (PP), buffer tablets was from Himedia, Ltd., Counting KIT-8 from Dojindo Laboratories Inc., Kumamoto, China, alcohol, hematoxylene, eosin, Dpx mount and xylene from Thomas Baker Pvt. Ltd., TNF-α and IL-1β rat ELISA protein assay kit from Invitrogen Pvt. Ltd. Solvents (NMR and GC/MS) and the chemicals used were of analytical grade. Milli-Q water was used throughout the study.

Animals and ethics statement: Female adult Sprague-Dawley (SD) rats (220-250 g) were procured from institutional animal house facility and kept in a 12 h day and 12 h night environmental condition at room temperature. All surgical interventions and post-operative animal care were carried out in accordance with the guidelines of care and use of rats Institutional Animal Experimentation Ethics Committee (Approval number XT2834921105) China for Animal Care and Use.

UV-Vis method for drug quantification: This method was established as per the previously reported literature by Chen *et al.*[10] with some modification. Briefly, known concentration of MP was scanned between 200 and 400 nm using UV-vis spectrophotometer in phosphate buffer containing 2% DMSO. The absorption maximum of this drug was observed to be at 244.5 nm. Furthermore, from the stock solution of MP (1 mg mL^{-1}) various dilutions were prepared of various strengths i.e., 5-50 μg mL^{-1} in phosphate buffer+DMSO (2%). Absorbance of the dilutions was taken at 244 nm and the calibration curve was plotted. Linearity was found between 5 and 35 μg mL^{-1} [10].

Preparation of multilayer nanoemulsion: The MSLNs were prepared by the pre-emulsion technique followed by the ultrasonic probe sonication method with the modified procedure i.e., previously used by Shrotriya *et al.*[11]. The MP and lipophilic surfactant (Span 80) were added in melted solid lipid (Precirol ATO 5). The aqueous surfactant (Tween 20) solution was prepared separately in 50 mL water. Both mixtures were kept at the controlled temperature above 60°C (>melting point of lipid). The aqueous surfactant solution was added in the lipidic mixture at the same temperature and stirred continuously using a high speed homogenizer (IKA T25 digital Ultra Turrax) at the speed of 4000 rpm for 1 h. The resulting emulsion was further sonicated using an ultrasonic probe sonicator (Sonics-Vibra Cell ultra-sonicator) for 15 min at pulse the pulse of 15 sec On and 5 sec Off. The final dispersion was cooled at room temperature to obtain the MSLNs.

Characterization of MSLN: Entrapment efficiency of MSLN was determined using fixed quantity of MSLN in a volumetric flask followed by extracting with the help of methanol. Samples were homogenized for 15 min and aliquot of the extracted MSLN was filtered using 0.45 μm PTFE filters. Filtered aliquot was mixed with four folds higher amount of water and vortexed for 2 min. The mixture was kept in study state for 10 min. Sample was used to take the reading of absorbance at 244.5 nm using UV-Vis spectrophotometer in order to quantify the dissolve MP concentration. Particle size and zeta potential of MSLN were determined by DLS (Malvern, U.K). Internal morphology along with dimension of the developed MSLN was confirmed using transmission electron microscopy (TEM, JEOL, Tokyo, Japan) by clicking digital images at 6000X[12].

Hydrogel synthesis: Emulgel of MSLN (MSLNG) of the desired viscosity and clarity was prepared by pH sensitive gelling of carbopol 940 (C940). About 1.5 wt% C940 was dispersed in the MSLN and kept as such for 24 h at room temperature to hydrate the polymer. Further the dispersion was stirred for 15 min at 400 rpm to ensure complete solubilization of C940 in MSLN. About 0.1 wt% of methyl paraben (preservative) was added in MSLN and C940 solution and pH was ensured between 6.5 and 7.4 using triethanolamine (pH adjuster; 400 μL). Gel of MP (MPG) was prepared using the same procedure. Placebo gel (PMSLNG) was prepared using the preparation procedure of MSLNG but it did not include MP.

Characterization of MSLNG: The prepared gel was subjected to measure the pH using pH meter at room temperature. Viscosity of the gel was measured by Brookfield Viscometer (DVLV-II+pro, UK) at 25±1°C and at 10 rpm speed using a spindle No. 61. Measurements were performed in triplicate.

***In vitro* drug release:** To investigate the amount of MP released from MSLNG, *in vitro* drug release study was carried out as per the procedure reported elsewhere. Briefly, a dialysis membrane of 50 KDa MWCO (Sigma-Aldrich Co, MO) was fixed between donor and receiver compartments of Franz diffusion cells. Cell was maintained at 37±0.5°C using a circulating water jacket. Accurately weighed quantity of the MSLNG and MPG (equivalent to 1 mg of MP) was placed in a donor compartment in such a manner that exhibit complete and intimate contact with dialysis membrane. The receiver compartment was filled with PBS (pH 7.4) containing 2% v/v DMSO. About 0.5 mL sample was withdrawn at predetermined time intervals (0.25, 0.5, 1, 4, 24, 48, 72, 96, 144 and 192 h) and

the receptor compartment was replaced with 0.5 mL fresh buffer. The samples were quantified for MP by UV-Vis spectrophotometer[13].

***In vitro* cytotoxicity study:** The viability and progress in proliferation of astrocytes were measured with the help of Cell Counting KIT-8 (Dojindo Laboratories Inc., Kumamoto, China). Various concentration of MP (i.e., 0.1-5%) were used in solution form (in DMSO) and in MSLN form to study their toxicological profile. These dilutions were added to the cultured astrocytes incubated in CCK-8 solution at 37°C for 2 h in 5% CO_2 rich incubator. Absorbance was measured at the wavelength indicated in the user's manual of the kit and the number of astrocytes was correlated with optical density[2].

***In vivo* implantation of NPSG:** The transverse section of the injured spinal cord was used to assess the effect of MSLNG and MPG implantation on SCI. The procedure is as follows. Animals were divided in to the groups of 10. Rats were anesthetized with the help of 10% chloral hydrate (3.5 mL kg^{-1}, i.p.) and placed on a hard base. The skin of rat was exposed along the midline of the back to show the vertebral column. Under aseptic conditions, T-9 laminectomy was carried out with the help of surgical microscope. After opening the dura mater about 2 mm piece of spinal cord was dissected to produce the SCI like environment. Finally was ensured complete removal of remaining tissue in the segment. Keeping first group as such, surgical sites of second and third group was transplanted with sterilized MSLNG and MPG, respectively. All the rats were surgically sutured with the help of 10-0 sterilized suture (Ethicon, Johnson and Johnson) and finally mussels and skin were closed[4]. During the study period, animals were assessed for behavioral changes at 2nd, 4th, 6th and 8th day of the study and animals were humanly sacrificed at 8th day to assess the histological changes and to estimate the level of increased level of inflammatory cytokines.

Estimation of inflammatory cytokines: Three rats were selected randomly from each group for Enzyme Linked Immunosorbent Assay (ELISA). About 1mm rostral and caudal part of spinal injury site was harvested. This study was carried out to quantify the expressed inflammatory mediators (IL-1β and TNF-α) in all the groups. For this purpose, tissues were homogenized in phosphate buffer, sonicated for 15 sec using the 5 sec off cycle in ice and kept at 4°C for 2 h. Samples were centrifuged at 1000 rpm for 10 min and the protein concentration was quantified using the supernatants using ELISA protein assay kit[14].

Behavioral assessment: Grid walking and beam walking tests were carried out to assess the recovery of sensory-motor functions after producing SCI. First group of animal was designated as SCI control group. Behavior of animals of MSLNG and MPG treated groups was observed for post implantation. Grid walking test was carried out using irregular horizontal wire cage. Animals were allowed to move for 4 min over the wire grid and observed at 2nd, 4th, 6th and 8th day after surgery. If entire hindlimb (all toes and heel) protruded completely through the grid, a misstep was counted along with the total number of steps taken. Data were expressed in the form of percentage of missteps. During beam walking, the total number of missteps of hindlimb was counted off the beam during animals crossing of the beam[2].

Histopathological analysis: After 8th day, rats were sacrificed by administering an overdose of anesthesia (ketamine 100 mg kg^{-1} and xylazine 20 mg kg^{-1}). The spinal cords were opened immediately post sacrifice and the mice were perfused with 4% paraformaldehyde in phosphate buffer saline (PBS) trans-cardially. Spinal cords were removed carefully and fixed using fixative at 4°C for 6-8 h. Samples were stored in 30% sucrose solution in PBS (pH 7.4) for 12 h. About 3 cm part of the spinal cords with injury epicenters and implanted material were dissected out. After embedding in optimal cutting temperature compound, samples were cut into 10 µm sections with the help of cryostat. Sections were stained using H and E dye and observed with the help of a light microscope. Histopathological damages were analyzed on the basis of neuronal vacuolation, inflammatory cell infiltration and hemorrhage[15].

Statistical analysis: Statistical analysis was performed using SigmaStat software (SPSS, Trial version, Developer IBM Corporation, New York). Data were compared between groups using a Student's t-test. In the case of unequal variances, the Mann-Whitney rank sum test was used. Differences with $p<0.05$ were considered significant.

RESULTS

Characteristics of NPS: Entrapment efficiency of MSLN was found to be 48.9%. Average particle size of MSLN was observed to be 76.7±7.8 nm with a polydispersity index (PDI) of 0.231 (Fig. 1). TEM study revealed uniform/smooth surface and nano size range of MSLNs. Zeta potential over MSLN surface was found to be -26.7 mV (Fig. 1).

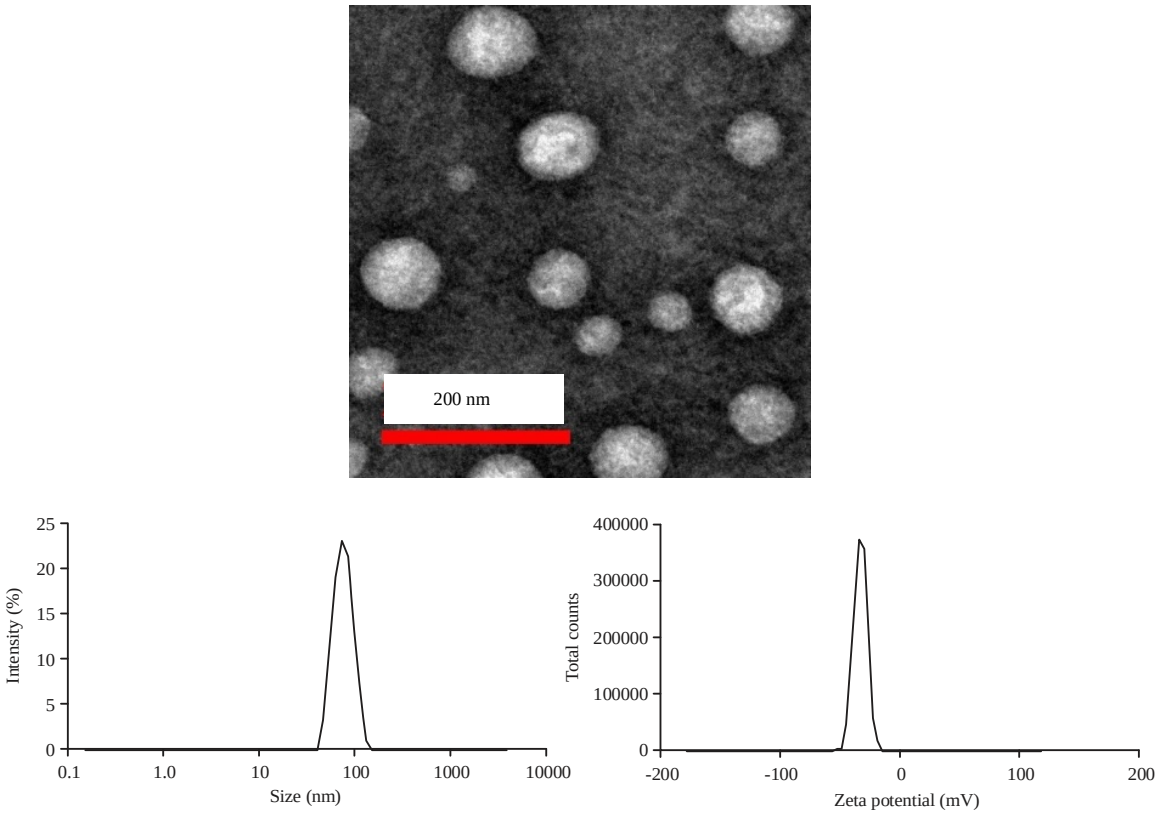

Fig. 1: TEM images to reflect shape, surface and internal structure of the prepared SLNs. Particle size of MSLN for the comparison of particle size distribution and zeta potential graph to reflect charge distribution over the surface of MSLN

Gelling of MSLN dispersion: pH sensitive gelling of MSLN was carried out using carbopol (C940) as gelling polymer and triethanolamine as alkalizer. After preparation, the gel was kept as such at room temperature for 24 h to remove air bubbles trapped in the gel matrix. Different batches were prepared to ensure required hardness and viscosity of the gel.

Characteristics of developed NPSG: MSLNG was characterized for pH and viscosity. The pH of the gel was maintained between 6.5-7.4. The desired pH was achieved using pH sensitive gelling of C940. Viscosity of MPG and MSLNG gels was found to be 82435±47.72 and 88205±47.72 cP, respectively.

***In vitro* drug release:** Controlled release of MP was observed from MSLNG. Rate of release of MP was observed to be slower in the case of MSLNG when compared with MPG. About 64.4% and 16.9% release of MP were observed in first 24 h of the study period from MPG and MSLNG, respectively. MPG released 99.5% of MP in just 96 h however, after 96 h, release of MP from MSLNG was observed to be 43.2% only. Burst release pattern of MP was observed initially from MPG, however, in the case of MSLNG it was found to be consistent throughout the study period (Fig. 2).

Effect of MP on cultured astrocytes and neurons: Effect of various concentration of MP in solution and MSLN on viability of astrocytes was assessed using CCK-8 assay. No cytotoxicity was observed on astrocytes at the concentration 1% of MP containing solution and MSLN however at 3% significant inhibition of the proliferation of astrocytes was observed in the case of MP solution when compared with MSLN at the same concentration. At 5% concentration, significant cytotoxicity in astrocytes was observed in both the samples as solution (viability 59%) and MSLN (viability 83%) (Fig. 3) showed reduction in cell viability. The MP solution was found to be more toxic than that of MSLN at the same concentration. No significant change in viability of the cells was observed in the case of vehicle control. At the therapeutic dose of MP, no toxicity was observed in both solution and MSLN.

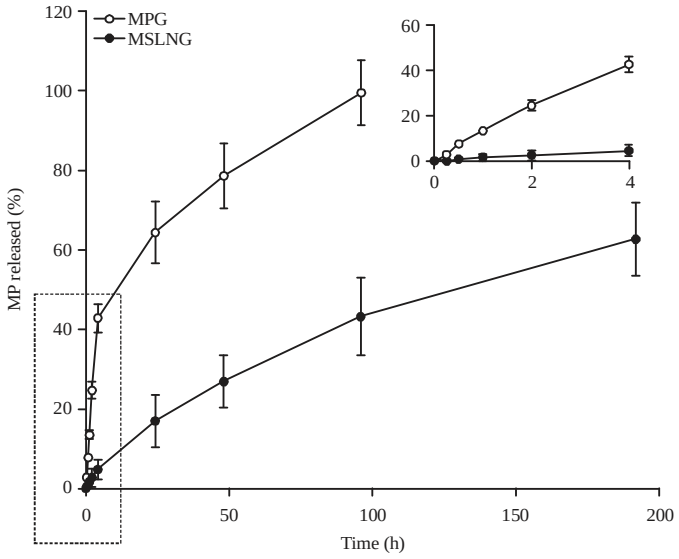

Fig. 2: *In vitro* MP release from MPG and MSLNG

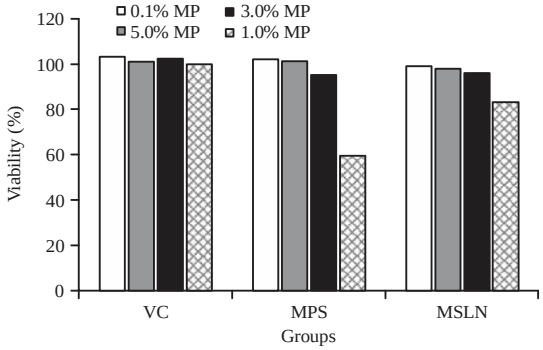

Fig. 3: *In vitro* cell viability study to assess cytotoxic potential of different concentration of MP either in solution form (MPS) or in nanoemulsion (MSLN)

Behavioral changes: The results of grid and beam walking tests at different time points (2nd, 4th, 6th and 8th day after injury) are illustrated in (Fig. 4a,b). In the beam walking test, MSLNG treated groups performed considerably better than that of MPG at all time points. In the grid walking test also the performance of MSLNG treated animal was better than the MPG at all time points. MSLNG treatment has improved functional outcomes of the animals only in 8 days (Fig. 4).

Level of cytokines in different groups of animals: Result of ELISA based quantification portrayed significant alleviation in the level of IL-1β and TNF-α by MPG and MSLNG than that of the control group (Fig. 5). The MSLNG was found the significant alleviation in the level of cytokines when compared with that of MPG where difference was observed to be non-significantly different when compared to that of SCI control.

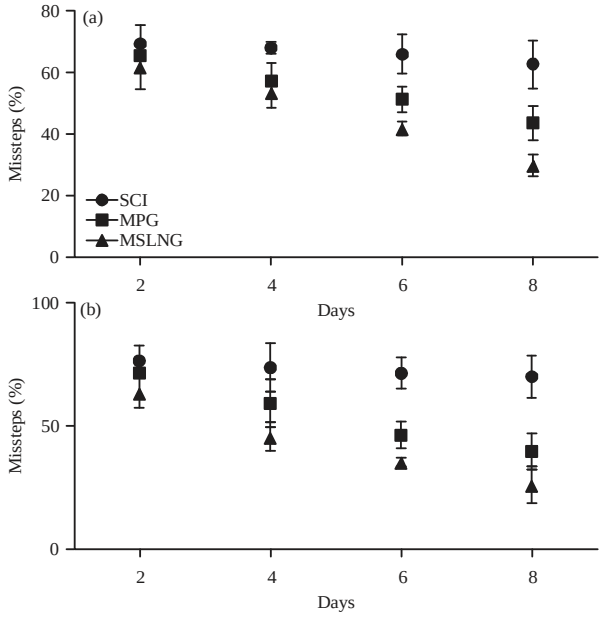

Fig. 4(a-b): Modulation of behavior of rats in terms of grid walking and beam walking after administering MPG and MSLNG in spinal cord injured rat

Histopathological modifications: Rats were humanly killed after 8th day of the study period of the implantation of MPG and MSLNG and examined for histological improvement as compared to SCI control rats using longitudinal sections. SCI control group consisted intense inflammatory cell infiltration, hemorrhage and larger pseudocyst. In MSLNG group the integrity of the spinal cord was reestablished efficiently (Fig. 6). The rheological properties of the MSLNG allowed it to stay for longer duration in contact with the injured site. A

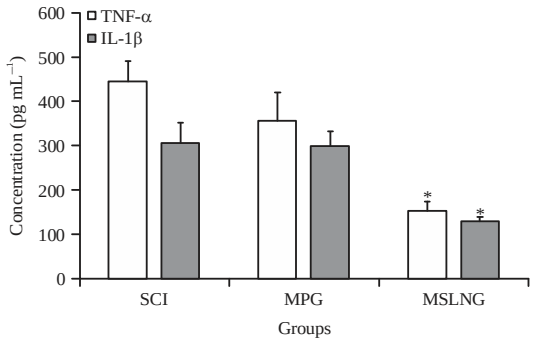

Fig. 5: Level of cytokines in SCI mice treated with MPG and MSLNG

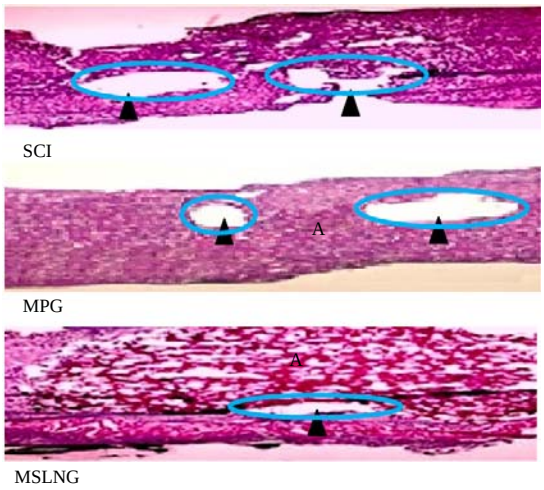

Fig. 6: Representative histopathological images of injured spinal cords (SCI, MPG and MSLNG, respectively) with and without treatment

noteworthy reduction in the volume of the pseudocyst, intensity of the inflammatory cell infiltration and hemorrhage was observed after the administration of MSLNG and MPG as compared to SCI control group however, MPG was observed to be less efficacious than that of MSLNG.

DISCUSSION

Effectiveness of oral Methylprednisolone is observed to be limited even it has very high bioavailability. This is due to the very high protein binding (about 78%). Most of the MP gets bind with the proteins present in flowing blood and does not get accumulated in sufficient quantity at SCI sites. This is considered as the main reasons behind the lower efficacy of MP in the treatment of SCI. Higher protein binding in the systemic circulation and inadequate site specificity offer an opportunity to the researchers to improve its potency. When talk about intravenous administration of MP, it is used in higher dose for systemic delivery (30 mg kg^{-1} bolus and 5.4 mg kg^{-1} h^{-1} infusion up to 24 h)[4]. However, the use of MP in higher dose expresses various side effects which might lead into the fluctuation of dose of MP in systemic circulation and hence into lesser recovery of the injured site. Therefore, local administration could help to improve the site specificity and higher availability at the desired site of action. At the same time, SLN could help control the release of MP so as to avoid the dose related toxicity. MSLNG for local administration and sustained release of MP over the injured site was developed. Biodegradable, lipid polymer-based MSLNG showed various potential advantages over conventional systemic delivery such as better effectiveness, control release and avoidance of first pass metabolism of MP after oral delivery etc. Significantly lower dose of MP was used to prepare MSLN. The therapeutic effectiveness of MP was improved by virtue of its local and sustained delivery.

Figure 3 shows the profile of MP releases from MSLNG in DW containing 2.0% (v/v) DMSO as co-solubilizer. Figure 3 reveals the release profile that exhibits no burst MP release as observed in the case of MPG. Less than 27% of MP release was observed in 48 min where MPG released 48% of the loaded drug. This type of sustained release profile of MP types drugs are also reported elsewhere. This is mainly due to the controlled diffusion of MP from the lipid matrix of SLNs into aqueous media. However, gel of pure MP is not able to control the release as efficiently as MSLNG. This release may be attributed to MP which matrixed in gel network which instantly release drugs at the site. Slow release of MP from MSLNG would give us confidence that lycopene could penetrate into the cellulose pores[16]. Lesser value of PDI as revealed in the case of MSLN, shows the uniform size distribution which might help in efficient absorption through the biological membrane. The electrical charge on the primary emulsion droplets was negative. The anionic charges over MSLN might give less interaction with the skin and result in to low biological interaction. But due to the smaller particle size and uniform distribution their penetration is supposed to be higher. The pH of developed gel was ensured between 6.5 and 7.4 so that the isotonicity with the site of administration can be maintained while planting this gel.

Gelling polymer like C940 is known to be the best vehicle for drug dispensing. Semisolid texture of MSLNG might retain the MSLN particles at the injured site for longer duration. The pH of the gel was ensured between 6.5-7.4 so as to maintain isotonicity of the gel formulation with the internal environment. Viscosity of the MSLNG was ensured similar to jelly that get adhered with the surface and do not move.

MSLNG was considered very favorable for the local administration and delivery of MP to the injury site[17]. The MSLNG might ensure long term availability of MP at the injury site which may decrease in the progression of secondary injury as a consequence of primary injury was observed.

The MSLNG was able in reducing cytotoxicity produced by MP solution at the same dose which might attributes to the sustained release and consistent diffusion of well-balanced quantity of MP into the media. The MSLNG avoided the instant delivery of the drug to the cells[18]. Cytotoxicity reducing capability of MSLNG suggests its utility in *in vivo* conditions also.

Significant decrease in IL-1β and TNF-α level of SCI injured rats by MSLNG was attributed to the improved drug delivery by controlling drug release at the site of administration. It was observed that, sustained delivery of MP over the injured site significantly decreased the lesional volume and improved the functional outcomes of SCI injured rats. The MP has performed better in MSLNG when compared its efficacy in MPG. MSLN is thought to be diffused from MSLNG and got in contact with the biological environment of the injured site (pH 7.2). This is supposed as the main mechanism of drug delivery over the biological site. These results were obtained at about ten folds lower dose of the conventionally administered dose (5.4 mg/animal). Development of MSLNG is offering an alternative treatment strategy for SCI like conditions. It is not only decreasing the lesional volume but promoting the proliferation of axons and ingrowth of blood vessels also.

CONCLUSION

Present study highlights the usefulness of lipophilic surfactant (Span 80) and solid lipid (Precirol ATO 5) based solid lipid nanoparticles in the delivery of MP to the post SCI site in a very controlled manner. Higher degree of protein binding leads to limited efficacy of MP when it injected to the blood circulation. Therefore, its local administration in the form of SLN could be proved as the superior alternative to the various oral and parenteral approached of drug delivery. It might also overcome the dose related toxicity associated with MP as this technique is achieving therapeutic level of the MP even after 10 folds reduction in its dose. Therefore, MSLNG might prove itself as a cost effective, safe, efficacious and clinically pertinent novel dosage form for the potential delivery of MP at SCI site. Further, this investigation provides an opportunity to the investigators working in the area of spinal cord injury.

SIGNIFICANCE STATEMENT

This study discovers the novel means of treating post SCI trauma like conditions by Methylprednisolone solid lipid nanoparticles (MSLN) based semisolid hydrogel after local administration. It can be beneficial in ensuring maximum Methylprednisolone (higher protein binding if administered orally or intravenously) availability at the spinal cord injury site even at much lower dose. This study will help researchers to uncover the critical areas of local delivery of different drugs by solid lipid nanoparticles in a semisolid vehicle which might offer safe and effective mean for the treatment of post SCI like conditions that many researchers were not able to explore. Thus, a new theory on local delivery for post SCI like conditions as an alternative to the intravenous and oral delivery systems may be arrived at.

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