Contents lists available at UGC-CARE

International Journal of Pharmaceutical Sciences and Drug Research

[ISSN: 0975-248X; CODEN (USA): IJPSPP]

Available online at www.ijpsdronline.com

Research Article

Formulation and Characterization of Imatinib Mesylate Liposomes in Gel for Intraarticular Administration

Amruta Gorajiya, Pragna Shelat, Anita Lalwani*

Department of Pharmaceutics, K. B. Institute of Pharmaceutical Education and Research, Kadi Sarva Vishwavidyalaya, Gujarat, India

ARTICLE INFO

Article history:

Received: 20 April, 2022

Revised: 14 August, 2022

Accepted: 22 August, 2022

Published: 30 September, 2022

Keywords:

Arthritis, Imatinib mesylate, Intra-articular injection, *In-vitro* release, Liposome, Xanthan gum gel.

DOI:

10.25004/IJPSDR.2022.140508

ABSTRACT

Intra-articular administration of drug loaded in liposomal gel directly in joints provides spatial and prolonged local action by minimizing drug particle clearance from the synovial cavity. The objective of the present study was to prepare imatinib mesylate (IMT) containing liposomes, which were further loaded in xanthan gum gel for intraarticular administration to increase the duration of drug release. Liposomes were prepared by using different ratios of 1,2-Dierucoyl-sn-glycero-3-phosphatidylcholine, 1,2-Dipalmitoyl-sn-glycero-3-phospho-rac-glycerol and cholesterol using thin film hydration method. The liposomes were evaluated for entrapment efficiency, surface charge potential and size distribution to establish formulation composition and process parameters. Light microscopy and scanning electron micrographs of the liposomes showed the spherical topography of the prepared liposomes. Viscosity and gel strength of the gel loaded with IMT containing liposomes was evaluated. *In-vitro* release study showed that liposome gel formulations could significantly extend the drug release compared with conventional gel and liposome formulations. The formulation was studied for stability over a period of 6 months for pH, viscosity, drug release up to 7 days at two different conditions i.e. 2 to 8°C and 25 ± 2°C and 60% RH ± 5% RH. Analytical results are more promising and no significant difference was observed in these parameters when the formulation was stored at 2 to 8°C. In summary, liposome gel is expected to be an efficient cargo for intra-articular drug delivery of Imatinib mesylate.

Introduction

Rheumatoid arthritis (RA) is a chronic progressive disease, causing extensive morbidity and mortality. It is an autoimmune disease that mostly affects the synovial tissue in multiple joints. In rheumatoid arthritis synovial tissue is characterized by an increased number of synovial fibroblasts and infiltration of macrophages and lymphocytes.[1,2] Imatinib mesylate targets protein tyrosine kinases such as abl, c-Kit, and platelet-derived growth factor receptor, and is widely used to treat chronic myeloid leukemia and c-kit-positive gastrointestinal stromal tumors. [3,4] Imatinib mesylate has been shown to be effective in severe RA with marked improvement in the joint pain and serum C-reactive protein (CRP) levels.[5,6]

Due to the localized nature of the joint, intraarticular (IA) injections are favored for treatment in rheumatoid arthritis. It has an edge over the other routes of administration as the systemic side effects are kept away. Additionally, systemic RA regimens fail to attain effective drug levels at the affected joints. Many drugs are available for the treatment of the rheumatic diseases but the number of the intraarticular products is restricted. At present there are only formulations with hyaluronic acid or glucocorticoid on the market.[7]

The not-so-widespread use of intraarticular route may be attributed to several problems, one of them being the pharmacokinetic aspect.[8] Some of the active compounds, based on their physicochemical properties, are rapidly cleared from the synovium, as the ultra-structure poses

***Corresponding Author:** Dr. Anita Lalwani

Address: K. B. Institute of Pharmaceutical Education and Research, Kadi Sarva Vishwavidyalaya, Gujarat, India

Email ✉: anita.lalwani@kbiper.ac.in

Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

little resistance to the diffusion of molecules through a joint.[9] The pharmacokinetics of the intraarticular route is comparable to that of intramuscular route as regards the rapid redistribution of the drug into the systemic circulation.[10] Thus, the intraarticular injection offers duration of action in the target tissues. This necessitates frequent injections, which in turn increase the risk of infection and noncompliance at patients' end.

To address the issue of the leaky structure of synovium, the drug may be trapped in the carrier system of a size that impedes the efflux from the joint. The retention of a system in joints is directly proportional to its size; the larger the size the greater the retention.[11] Drug delivery systems having a size less than 250 nm rapidly diffuse from the joint cavity.[12] While systems in a size range of 1 to 10 microns are engulfed by synovial macrophages, without initiating a neutrophil response.[13] Pradal *et al*. reported complete retention of MPs of particles with mean diameter of 10 µm, regardless of the inflammatory condition of the joint. [14] Biodegradable microparticles have been researched for prolonged duration of action for the intraarticular administration. Lornoxicam loaded chitosan microparticles (3.5–6.1 µm) showed prolonged anti-inflammatory effect as compared to the drug solution. FX006, triamcinolone acetonide-loaded poly (lactic-co-glycolic acid) (PLGA) MPs have been approved by USFDA under the brand name Zilretta, for use in osteoarthritis as an intraarticular injection. The product gives a prolonged action for a period of 3 months.[15]

Liposomes are worthy carriers for the local delivery of drugs through intraarticular route to prolong the duration of action and decrease the systemic side effects.[16-17] Incorporation of liposomes in gels further increases the duration of drug release and the stability of the system.[17-18] Gels may be composed of carbopol and sodium carboxymethyl cellulose have been used to incorporate diclofenac sodium loaded liposomes and these have proved to elongate the residence time in knee joints using radiolabeled diclofenac sodium.

In the present investigation IMT liposomes were prepared using dry lipid[10] film formation technique by using rotary evaporator. Different formulation compositions variables *i.e.* 1,2-Dierucoyl-sn-glycero-3-phosphatidylcholine (DEPC) concentration and cholesterol concentration were evaluated with reference to entrapment efficiency. Additionally, different process parameters like temperature, time, RPM and vacuum of the rotary evaporator for solvent removal process were optimized to get maximum entrapment efficiency. The optimized liposomes containing IMT were incorporated in xanthan gum gel.

Table 1: Optimization of ration of lipid concentration.

Batch no.	*DEPC (mg/mL)*	*Cholesterol (mg/mL)*	*Entrapment efficiency (%)*
IMGL-1	8	3	26.9
IMGL-2	8	5	30.1
IMGL-3	10	5	47.5
IMGL-4	12	5	70.3
IMGL-5	10	8	58.6
IMGL-6	12	8	66.9

Materials And Methods

MATERIALS

Lipids 1,2-Dipalmitoyl-sn-glycero-3-phospho-rac-glycerol sodium (DPPG-Na) and 1,2-Dierucoyl-sn-glycero-3-phosphatidylcholine (DEPC) bought from lipoid GmbH, USA. Cholesterol was obtained from Dishman, India. Imatinib mesylate purchased from the Shilpa Medicare, India. Propylene glycol, boric acid, chromatographic grade acetonitrile were purchased from Merck reagents (USA). Xanthan gum obtained from C P Kelco (India). Purified water was prepared in the laboratory. All other reagents and solvents used in liposome gel were of analytical grade.

Preparation of Liposome

Thin film hydration method used to prepare IMT liposomes. DPPG-Na, DEPC and cholesterol were dissolved in dichloromethane. The lipid mixture was then mixed to get clear solution and transferred into round bottom flask to evaporate organic solvent and prepare dry lipid film in a Rotary evaporator (Heidolph, Hei-vap, Germany). Traces of organic solvent were removed by using 50–150 mbar vacuum for 45 minutes at 150 rpm and 37°C. Dry lipid film was hydrated by using IMT aqueous solution for 2 hours above the lipid transition temperature (at room temperature). The liposomal dispersion thus obtained was homogenized at 10,000 rpm by using polytron (Kinematica AG, Model MT 5100 S) for 15 minutes. Liposomal dispersion was extruded using lipid extruder (Northern Lipid Inc., Model: LIPEX™ 800mL-STBX-HB) through polycarbonate filters (Whatman Neuclepore, pore size of 200 nm). Liposomal dispersion was then filtered with 0.2 µ polyether sulfone (PES) membrane filter (Sartorius Stedim) and stored at 2 to 8°C for further process and evaluation.

Preparation of Xanthan Gum Gel

The xanthan gum solution (3% w/v) was prepared by adding xanthan gum slowly under stirring in glass vessel that contained boric acid, propylene glycol and water to get clear solution. Xanthan gum solution was hydrated using continuous stirring and at 40°C temperature for 2 hours, the solution was then filtered through 0.6 µ filter (FTKJK006, PALL) for clarification purpose. Filtered phase was further sterilized at 121°C for 15 minutes by using steam sterilizer (Autoclave, Machin fabrik).

Preparation of Liposomal Gel

The required quantity of xanthan gum phase (3% W/V) and liposome dispersion were mixed to get homogeneous

Table 2: Optimization of process parameters

Formulation	*Time (Hr)*	*Temperature (°C)*	*RPM*	*Vacuum (mm Hg)*	*Entrapment efficiency(%)*
IMGL-7	4	37 ± 2	100	300	70.1
IMGL-8	6	37 ± 2	150	300	74.3
IMGL-9	6	37 ± 2	150	200	78.2
IMGL-10	15	37 ± 2	150	200	81.5
IMGL-11	6	37 ± 2	150	200	86.2
IMGL-12	6	37 ± 2	150	100	94.1

Table 3: Composition of imatinib mesylate liposome gel batch IMGL-16.

S. no	*Ingredients*	*Conc. (mg/mL)*
	Iimatinib mesylate	5.0
	Cholesterol	5.0
	DPPG Na	1.0
	DEPC	15.0
	DCM	q.s.
	Propylene glycol	5.0
	Xanthan gum	3
	Boric acid	1.5
	Glucose	35
	L-lysine	10
	Water	q.s.

gel dispersion by using simple mixer (IKA, RW 20). Water was added to it to get 1-mg/mL IMT liposomal gel containing 1% xanthan gum gel phase. Bulk was stored at 2 to 8°C till further evaluation.

Particle Size Distribution

The particle size distribution of IMT liposomal gel dispersion was measured by using a zetasizer (NanoZS, Malvern, UK) at temperature of 25°C. The particles diffuse at a speed with respect to their size, smaller particles diffusing faster than larger particles. By measuring Brownian movements, diffusion rate of particles in a sample, hydrodynamic diameter can be determined by zetasizer. To achieve desired count rate level, liposomes were diluted with purified water and sonicated before the measurement. At an angle of 173°, the intensity of the light scattered by the particles was sensed. From this evaluation, the z-average and PDI were determined.[20-21]

Surface Charge Potential

The electrical charge stability of lipid bilayer in liposome dispersion system was quantified by measuring the zeta potential (surface charge potential). The zeta potential was determined by measurement of the electrophoretic mobility (25°C) using Zeta Seizer (Nano ZS, Malvern Instruments, UK). Sample was prepared by diluting liposome with purified water. Sample was taken in specific cuvette and ensured no any air bubble was present before analysis at room temperature.[22]

HPLC Analysis of Imatinib Mesylate

The HPLC system comprised of auto sampler, binary pump, and 2489 UV-visible detector (Waters, USA). The mobile phase consisting of acetonitrile, water (30:70) was pumped through the Inertsil/ODS C18 (4.6 mm × 250 mm × 5 µm) at a flow rate of 1.0-mL/min and the eluent was monitored at 260 nm. [23]

Determination of %Drug Entrapment Efficiency

IMT liposome (5 mL) formulation was transferred to the internal compartment of Amicon® centrifuge tubes fitted with an ultrafilter (molecular weight cut-off 10 kDa, Merck Millipore) and processed for centrifugation at 9000 rpm for 45 minutes. The aqueous phase (filtrate) wascollected at the lower compartment of ultrafilter membrane tube and subjected to high-performance liquid chromatography (HPLC) analysis to quantify the IMT content. In order to confirm the total amount of drug present in the system, IMT liposome formulation was diluted appropriately with methanol to disrupt the liposome particle, releasing the drug into the solution and then final clear solutions were examined for drug content by HPLC. The entrapment efficiency was calculated as the percentage of drug entrapped to the total drug.

Residual Solvent Analysis by Gas Chromatography

Residual solvent concentration was detected by using gas chromatography (GC). The liposomal dispersion (0.5 mL) was taken in a GC head space 20 mL glass vial and diluted with 5 mL distilled water. GC column (DB-624; Dimensions, L: 60 m, D: 0.53 mm, Agilent Technologies, Japan) was used. By using a micro-syringe heated to 65°C, the gas phase was evaporated from the vial and quantified by GC.[24]

Scanning Electron Microscopy (SEM)

SEM images were captured by using scanning electron micrograph (magnification: 10,000; accelerating voltage: 20.0 kV, Jeol, Japan). The liposomes were diluted and freeze at 20°C and then placed on the grid of sample holder. After the samples were placed and vacuum was applied, the images were recorded.

Light Microscopy

By using Linkam FDCS196 freeze drying microscopy system (Nikon Eclipse LV100N POL, USA), morphology was evaluated. Sample was diluted 10 times with water

and single drop was added on slide and then covered with cover slip. At 50X (500 times magnification), sample was observed.

pH

The pH of IMT liposomal gel dispersion was measured by pH meter (Thermo Scientific™ Orion Star™ A121) at temperature of 25 ± 2°C.

Viscosity and Rheology

Viscosity of liposome gel formulations at initial optimization and on stability batches were evaluated by using cone & plate viscometer (CP52 spindle, Amtek, Brookfield). Rheology of IMT Liposome gel was evaluated by using Rheometer (Model: MCR302, Make: Anton PAAR). RheoCompass™ software was used for data analysis. For sample preparation, cone angle 1°, sample volume 1-mL poured on the surface of stage and cone and Plate geometry of spindle (CP-50-1) was used. Analysis was carried out at room temperature (25°C). The rheometer was used for the measurements of loss moduli G′ and loss modulus G".[25]

In-vitro Drug Release Studies by Bottle Rotating Apparatus

In-vitro release of drug from liposome gel formulations was evaluated by using dialysis membrane (Spectra-Por® Float-A-Lyzer® G2, Molecular weight cut off: 30 KD, Merck). The bottle rotating dissolution apparatus (Electrolab, India) was used to evaluate drug release profile in phosphate buffer media (PBS pH 7.4, 0.05% Na-azide solution, 0.5% Bovine serum albumin). In semipermeable membrane, 1-mL of the liposome gel formulation was placed and both the ends of bags were tied to prevent any leakage. Then, semipermeable membranes were gently placed in the bottles and mounted on holder. Bottles were rotated at 20 rpm for 7 days at 37.0 ± 0.5°C. At predetermined regular time intervals 1-mL of the sample was collected and replaced with an equal volume of the dissolution medium. The amount of IMT released in to the medium was determined with the help of UV spectrophotometry at a λ_{max} of 260 nm.

In-vitro Drug Release Studies in Simulated Synovial Fluid Media by Franz Diffusion Cell

The use of simulated synovial fluids (SSFs) is a promising *in-vitro* drug release method to predict the release mechanisms and possible *in-vivo* behavior of drug formulations. In the literature, the wide variety of SSFs described to replicate synovial environments. Synovial fluid composition was prepared as described by Margareth Marques et al. with slight modification. Three different formulations are tested and compared for drug release in simulated synovial fluid media by using Franz diffusion dissolution apparatus.[26-27]

These formulations are as per below:

Formulation A: API is mixed with 1% Xanthan gum gel phase as per prerequisite dose

Formulation B: Liposome dispersion formulation (without gel phase)

Formulation C: Liposome embeded gel formulation (liposome embedded in gel phase)

Stability Studies

The stability studies were conducted at different temperature conditions on optimized IMT loaded liposomal gel. A 1-mL product of IMT liposomal gel dispersion with drug concentration of 0.5 mg/mL was taken into glass pre filled syringe (PFS), stoppered with Flurotec plunger stopper and stored at 2 to 8°C and 25°C/60%RH for 6

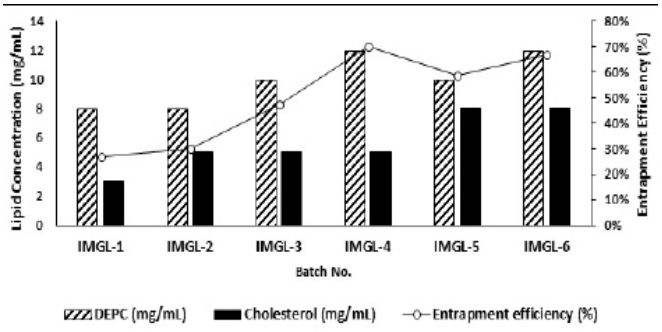


Fig. 1: %Drug efficiency with respect to different ratios of DEPC and cholesterol.

Fig. 2: Image of final packed product in siliconized glass 1-mL syringe with plunger stopper.

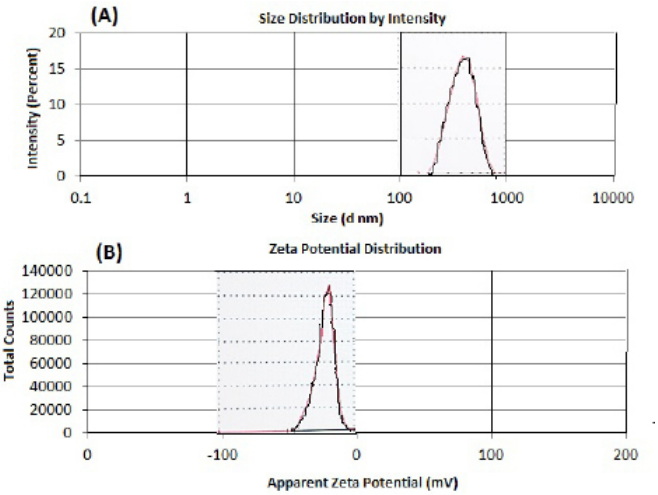
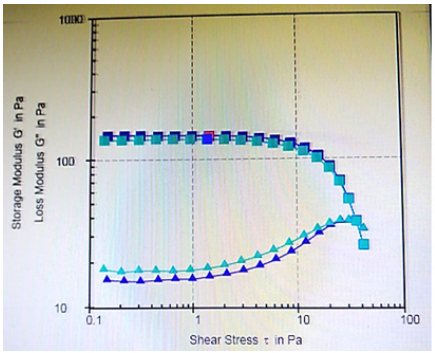


Fig. 3: (A) Particle size distribution (B) Zeta potential of formulation IMG12.



Viscosity	350 cP
Torque	45.2%
Speed	12 RPM
Temperatur	24.6?C
Time	00:00:20.0
SS	84.09 dyne/cm^2
SR	24.00 1/s
Density	0.0000g/cm^3
Accuracy	7.75 cP

Fig. 4: The sol-gel transition rheological behavior of IMT Liposomal gel (IMGL -16). Storage modulus (G′) and loss modulus (G″) as a function of shear stress τ).

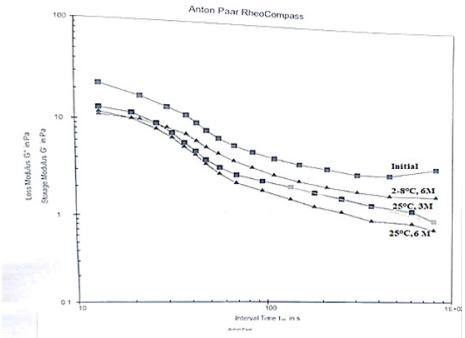


Fig 5: Rheology of IMT Liposomal gel (IMGL -16). A) Viscosity by cone and plate viscometer, B) Rheological behavior of different batches and C) Rheology of stability batch at different storage conditions

months. The stability assessment was evaluated on the basis of pH, particle size, viscosity, and %drug release in the dispersion, at different predetermined time points.[28-29]

Result And Discussion

For a preliminary screening study, optimization of formulation was done by evaluating various material attributes (lipid composition), process parameters (rotational speed of the rotary evaporator, time and the temperature). The drug entrapment efficiency was the key parameter that was evaluated for further optimization process.

It was observed that, rotational speed of rotary evaporator flask has significant impact on the thickness and uniformity of the lipid film. The optimum rotational speed was observed to be 150 rpm. To remove traces of organic solvent, the lipid film was kept overnight under vacuum.

Selection of Lipid to Drug Ratio

Different proportions of phosphatidyl choline (DEPC) and cholesterol were taken and % drug entrapment efficiency was calculated. Liposome film was formed at 37 ± 2°C, 200 mmHg vacuum and 150 RPM. Then film was hydrated with API containing aqueous phase and processed for size reduction by high pressure homogenization. Unentrapped drug was removed by centrifugation (Table 1). By altering the proportion of cholesterol and DEPC, drug entrapment efficiency varied significantly. Up to certain level, as the cholesterol concentration increased, entrapment efficiency also increased but after certain point entrapment efficiency decreased. The optimum concentration of DEPC and cholesterol was found 12 and 5 mg, respectively.

At increasing concentration of DEPC, drug entrapment efficiency also increased. But in case of cholesterol, drug entrapment efficiency increased up to certain level but further increase in concentration, interfered with the drug loading in the liposome structure. Formulation IMGL-4 had maximum entrapment efficiency and was finalized for further process optimization (Fig. 1).

Optimization of Solvent Evaporation by using Rota Evaporator

Thin film hydration method is widely used to prepare liposomes. Different processing conditions like vacuum, time speed were evaluated to form thin lipid film. Rotary evaporator method was further optimized for solvent removal. Based on of entrapment/encapsulation efficiency process parameters were optimized (Table 2).

Process parameters of IMGL-12 formulations support the maximum drug loading in liposome. The rate of solvent removal under vacuum conditions had significant impact on drug entrapment efficiency of liposome. Final bulk was packed in 1.0 mL siliconized glass PFS and stored at 2-8°C for further analysis (Fig. 2).

Optimization of Formulation and Process Parameters for Xanthan Gum

Particle Size Distribution

The average particle size of the liposomal dispersion was estimated to be 453.5 nm and polydispersity in IMT of 0.104 indicating uniform particle size distribution. (Fig. 3A) There was no significant change in the particle size of liposomes were observed when they are dispersed in xanthan gum gel phase.

Zeta Potential

The zeta-potential of the liposome preparation was -29 mV. (Fig. 3B) No significant variation was observed in the zeta potential value of liposomal gel formulations. It was observed in the range of -25 mV and -35 mV. Commonly, particles are stable above 30 mV or below −30 mV in their respective dispersion medium. Single sharp peak confirms uniform surface charge distribution on liposomes. Negative value of zeta potential indicates liposomes carries negative surface charge because of DPPG lipid. Due to surface charge potential, liposomes remain suspended in the dispersive media throughout the shelf life.

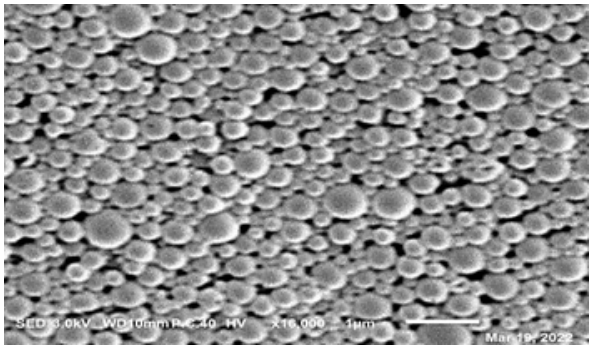


Fig. 6: Scanning electron microscopy of imatinib mesylate liposome (IMLG-16).

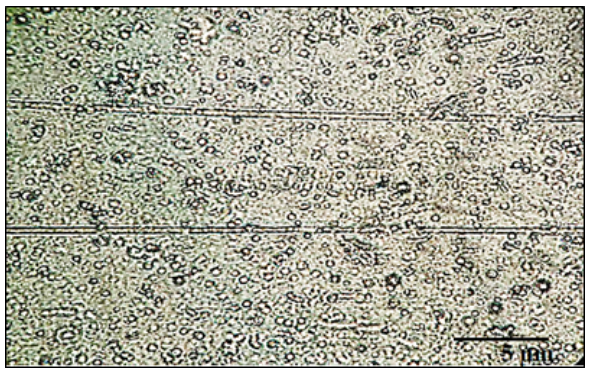


Fig. 7: Microscopy images of Liposome by Polarizing Freeze Dry Microscopy of IMLG-16.

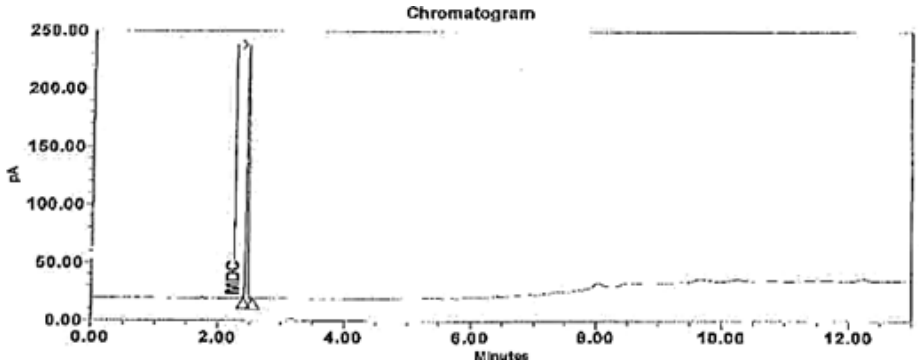


Fig. 8: Residual solvent chromatogram by GC of IMT Liposome gel (IMGL-16).

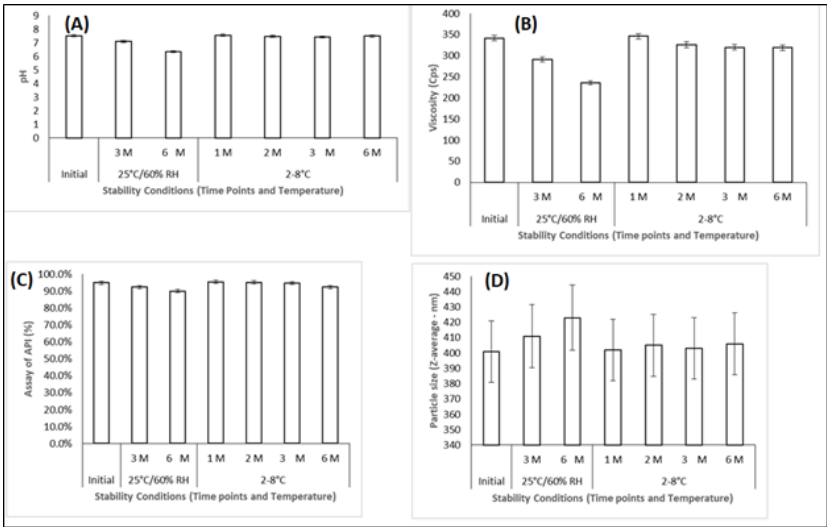


Fig. 9: Stability studies of IMLG-16 A) pH B)Viscosity C) %Entrapment Efficiency D)Particle size distribution (mean ± SD, n = 3).

Liposomal Gel Characterization

pH

pH of the liposomal gel formulation was found to be in the range of 5.5 to 7.5.

Viscosity and Rheology

The rheological characteristics of the Imatinib mesylate gel was evaluated as shown in Figs. 4 and 5. Initial the initial viscosity values observed around 350 ± 25 cps at 25°C. It was observed that gel strength value was 4.55 Pa. In other batches it was observed in the range of 4.2 to 5.5 Pa. Fig. 5 shows the storage modulus G' (elastic modulus) and loss modulus G'' (viscous modulus) of xanthan gum gel conferring to strain amplitude at a particular angular frequency. The value of G' is greater than G'', which indicates the sample behaves as a gel. Additionally, rheology with reference to storage modulus G' vs shear stress evaluated on stability batch IMGL -16.

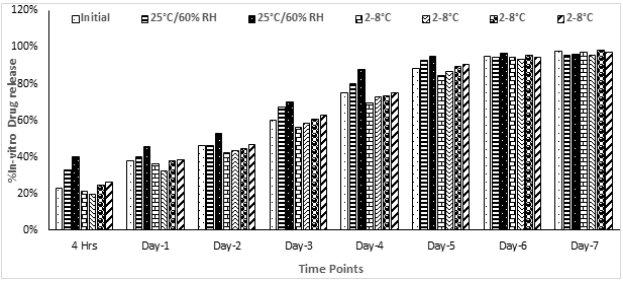


Fig. 10: Analytical % In-vitro release results of stability batch - IMLG-16 up to day 7.

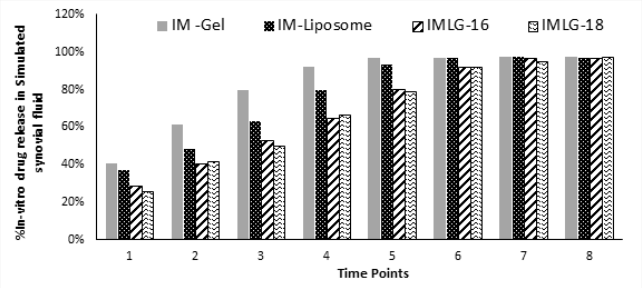


Fig. 11: *In-vitro* dissolution in simulated synovial fluid media by franz diffusion cell in API in gel (IM-gel), IM liposome, batch IMLG-16 and IMLG-18.

It was observed that storage modulus value is lesser at 25°C/60% RH compared to results observed at 2 to 8°C (Figs. 4 and 5).

Scanning Electron Microscopy (SEM)

The scanning electron micrograph of IMT liposome was shown in Fig. 6. SEM images shows that the particles are spherical in shape and have a uniform size distribution. The size of liposomes, detected by SEM analysis, was comparable with size distribution obtained from DLS method.[29]

Light Microscopy

Morphology was evaluated by light microscope shows particles are spherical and size distribution is submicron in range (Fig. 7).

Residual Solvent analysis by Gas Chromatography (GC)

As per ICH guidelines [Q3C (R8)], DCM is regarded as Class II solvent and recommendation for permitted daily exposures (PDE) are ≤ 6.0 mg/day (600 ppm). As per GC chromatograph (Fig. 6), IMT-liposome gel, DCM concentration was observed <250 ppm.

Stability Study of Liposome Gel

A stability study was carried out on liposomal gel formulations (IMLG-16). Final composition refers Table 3. Batch IMLG-18 prepared by using same composition and process parameters to confirm the reproducibility. Liposomes were filled in glass PFS and stored in horizontal state at 2 to 8 and 25°C/60% RH over duration of 6 months. From stability data, it was observed that pH value, viscosity, assay of API and particle size distribution (Z-average) changed significantly at 25°C/60%RH condition. Whereas there was no alteration in pH, Assay of IMT and viscosity at 2 to 8°C stability storage condition. First burst and drug release at the end of 4 days was higher at 25°C/60%RH as compared to 2 to 8°C (Figs. 9 and 10).

The magnitude of drug retention within the vesicles, during storage under predefined conditions, eventually describes the shelf life of the developed formulation. Drug leakage was higher, at higher temperatures condition, as observed in storage-stability studies. It recommended, storing the liposomal gel product in the refrigerated conditions, to minimize the drug leakage from liposomal-systems. Loss of entrapped drug from the vesicles, at elevated temperatures may be related to the effect of temperature on the gel to liquid transition of lipid bilayers transition and possible chemical degradation of the phospholipids, leading to defects in the membrane arrangement.

In-vitro Dissolution in Simulated Synovial Fluid Media

In simulated synovial fluid media, *in-vitro* drug release was conducted up to 7 days. It was observed that burst release was higher in IMT Gel and IMT Liposome compared to IMT liposomal gel formulation. Maximum drug released from IMT Gel and IMT Liposome (>80%) in 4 days. While in case of IMT liposomal gel formulation, while less than 80% drug released in 5 days. It can be concluded that xanthan gum gel phase provides additional sustained release effect from liposome phase (Fig. 11).

Conclusion

Liposomal gel drug delivery systems for Imatinib mesylate has been successfully optimized and developed by using thin film hydration method. The optimized IMT-liposomes having particle size 401 nm and spherical in shape. Liposomal gel as delivery system can play an important role in improving the need for developed delivery of IMT for targeted and local action. Optimization loading of IMT is not only dependent on the physico-chemical nature of these compounds, but also on factors such as the lipid ratio and the manufacturing method. Liposomal gel was found to be stable at 2 to 8°C temperature. In-vitro release data supports and proves the uniform and sustained drug release of liposomal gel carriers for targeting Intra articular route.

Conflict of Interest

The authors declare that there is no conflict of interests on the subject of the publication of this paper.

Acknowledgment

The author is obliged to Amneal Pharmaceutical, Ahmedabad for providing the laboratory facilities, chemicals to complete the research work.

Funding

None

Ethical Approval

Not applicable

Authors' contributions

This work was performed in collaboration by all authors. Author AG designed the study, performed the statistical analysis and wrote the first draft of the manuscript. Authors PS and AL managed the analyses of the study. Author AL managed the literature searches. All authors read and approved the final manuscript.

References

1. Feldmann M. Brennan, FM, and Maini, RN Rheumatoid Arthritis. Cell. 1996;85:1277-89. https://doi.org/10.1016/s0092-8674(00)81109-5
2. Firestein GS. Evolving concepts of rheumatoid arthritis. Nature. 2003 May;423(6937):356-61. https://doi.org/10.1038/nature01661
3. Druker BJ, Talpaz M, Resta DJ, Peng B, Buchdunger E, Ford JM, Lydon NB, Kantarjian H, Capdeville R, Ohno-Jones S, Sawyers CL. Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. New England Journal of Medicine. 2001 Apr 5;344(14):1031-7.. https://doi.org/10.1056/nejm200104053441401
4. Demetri GD, Von Mehren M, Blanke CD, Van den Abbeele AD, Eisenberg B, Roberts PJ, Heinrich MC, Tuveson DA, Singer S, Janicek M, Fletcher JA. Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. New England Journal of Medicine. 2002 Aug 15;347(7):472-80. https://doi.org/10.1056/nejmoa020461
5. Miyachi K, Ihara A, Hankins RW, Murai R, Maehiro S, Miyashita H. Efficacy of imatinib mesylate (STI571) treatment for a patient with rheumatoid arthritis developing chronic myelogenous leukemia. Clinical rheumatology. 2003 Oct;22(4):329-32.. https://doi.org/10.1007/s10067-003-0716-3
6. Eklund KK, Joensuu H. Treatment of rheumatoid arthritis with imatinib mesylate: clinical improvement in three refractory cases. Annals of medicine. 2003 Jan 1;35(5):362-7. https://doi.org/10.1080/07853890310001339
7. Ayral X. Injections in the treatment of osteoarthritis. Best practice & research Clinical rheumatology. 2001 Oct 1;15(4):609-26.. https://doi.org/10.1053/berh.2001.0177
8. Edwards SH. Intra-articular drug delivery: the challenge to extend drug residence time within the joint. The Veterinary Journal. 2011 Oct 1;190(1):15-21. https://doi.org/10.1016/j.tvjl.2010.09.019
9. Wigginton SM, Chu BC, Weisman MH, Howell SB. Methotrexate pharmacokinetics after intraarticular injection in patients with rheumatoid arthritis. Arthritis & Rheumatism: Official Journal of the American College of Rheumatology. 1980 Jan;23(1):119-22. https://doi.org/10.1002/art.1780230121
10. Park CW, Ma KW, Jang SW, Son M, Kang MJ. Comparison of piroxicam pharmacokinetics and anti-inflammatory effect in rats after intra-articular and intramuscular administration. Biomolecules & Therapeutics. 2014 May;22(3):260. https://doi.org/10.4062/biomolther.2014.037
11. Bonanomi MH, Velvart M, Stimpel M, Roos KM, Fehr K, Weder HG. Studies of pharmacokinetics and therapeutic effects of glucocorticoids entrapped in liposomes after intraarticular application in healthy rabbits and in rabbits with antigen-induced arthritis. Rheumatology international. 1987 Sep;7(5):203-12. https://doi.org/10.1007/bf00541378
12. Levick JR. A method for estimating macromolecular reflection by human synovium, using measurements of intra-articular half lives. Annals of the rheumatic diseases. 1998 Jun 1;57(6):339-44. https://doi.org/10.1136/ard.57.6.339
13. Champion JA, Walker A, Mitragotri S. Role of particle size in phagocytosis of polymeric microspheres. Pharmaceutical research. 2008 Aug;25(8):1815-21. https://doi.org/10.1007/s11095-008-9562-y
14. Pradal J, Maudens P, Gabay C, Seemayer CA, Jordan O, Allémann E. Effect of particle size on the biodistribution of nano-and microparticles following intra-articular injection in mice. International journal of pharmaceutics. 2016 Feb 10;498(1-2):119-29. https://doi.org/10.1016/j.ijpharm.2015.12.015
15. Microsphere [Available from: https://zilretta.com/about-zilretta/the-microspheres. assessed on 20 August 2022]
16. Türker S, Erdoğan S, Özer YA, Bilgili H, Deveci S. Enhanced efficacy of diclofenac sodium-loaded lipogelosome formulation in intra-articular treatment of rheumatoid arthritis. Journal of drug targeting. 2008 Jan 1;16(1):51-7. https://doi.org/10.1080/10611860701725191
17. Butoescu N, Jordan O, Doelker E. Intra-articular drug delivery systems for the treatment of rheumatic diseases: a review of the factors influencing their performance. European Journal of Pharmaceutics and Biopharmaceutics. 2009 Oct 1;73(2):205-18. https://doi.org/10.1016/j.ejpb.2009.06.009
18. https://doi.org/10.1016/s0378-5173(02)00221-1
19. Türker S, Erdoğan S, Özer AY, Ergün EL, Tuncel M, Bilgili H, Deveci S. Scintigraphic imaging of radiolabelled drug delivery systems in rabbits with arthritis. International journal of pharmaceutics. 2005 May 30;296(1-2):34-43.
20. Epstein H, Gutman D, Cohen-Sela E, Haber E, Elmalak O, Koroukhov N, Danenberg HD, Golomb G. Preparation of alendronate liposomes for enhanced stability and bioactivity: in vitro and in vivo characterization. The AAPS journal. 2008 Dec;10(4):505-15. https://doi.org/10.1208/s12248-008-9060-5
21. Singh P, Bodycomb J, Travers B, Tatarkiewicz K, Travers S, Matyas GR, Beck Z. Particle size analyses of polydisperse liposome formulations with a novel multispectral advanced nanoparticle tracking technology. International journal of pharmaceutics. 2019 Jul 20;566:680-6. https://doi.org/10.1016/j.ijpharm.2019.06.013
22. Smith MC, Crist RM, Clogston JD, McNeil SE. Zeta potential: a case study of cationic, anionic, and neutral liposomes. Analytical and bioanalytical chemistry. 2017 Sep;409(24):5779-87. https://doi.org/10.1007/s00216-017-0527-z
23. Gupta B, Poudel BK, Pathak S, Tak JW, Lee HH, Jeong JH, Choi HG, Yong CS, Kim JO. Effects of formulation variables on the particle size and drug encapsulation of imatinib-loaded solid lipid nanoparticles. Aaps Pharmscitech. 2016 Jun;17(3):652-62. https://doi.org/10.1208/s12249-015-0384-z
24. Kanda H, Katsube T, Goto M. Preparation of liposomes from soy lecithin using liquefied dimethyl ether. Foods. 2021 Aug 2;10(8):1789. https://doi.org/10.3390/foods10081789
25. Thai LP, Mousseau F, Oikonomou EK, Berret JF. On the rheology of pulmonary surfactant: effects of concentration and consequences for the surfactant replacement therapy. Colloids and Surfaces B: Biointerfaces. 2019 Jun 1;178:337-45. https://doi.org/10.1016/j.colsurfb.2019.03.020
26. Marques MR, Loebenberg R, Almukainzi M. Simulated biological fluids with possible application in dissolution testing. Dissolution Technol. 2011 Aug 31;18(3):15-28.
27. D'Souza S. A review of in vitro drug release test methods for nano-sized dosage forms. Advances in Pharmaceutics. 2014 Nov 20;2014.
28. Hadian Z, Sahari MA, Moghimi HR, Barzegar M. Formulation, characterization and optimization of liposomes containing eicosapentaenoic and docosahexaenoic acids; a methodology approach. Iranian journal of pharmaceutical research: IJPR. 2014;13(2):393.
29. Cho HY, Lee CK, Lee YB. Preparation and evaluation of PEGylated and folate-PEGylated liposomes containing paclitaxel for lymphatic delivery. Journal of Nanomaterials. 2015 Jan 1;2015.

HOW TO CITE THIS ARTICLE: Gorajiya A, Shelat P, Lalwani A. Formulation and Characterization of Imatinib Mesylate Liposomes in Gel for Intraarticular Administration. Int. J. Pharm. Sci. Drug Res. 2022;14(5):559-566. **DOI:** 10.25004/IJPSDR.2022.140508