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Peyer'e patch targeting of Isradipine loaded Solid Lipid Nanoparticles: It's cellular uptake study

Jagruti B. Prajapati[a,*], Hitesh Katariya[b], Ravish Patel[a]

[a] Ramanbhai Patel College of Pharmacy, Charotar University of Science and Technology, CHARUSAT Campus, Changa, 388421, Dist. Anand, Ta. Petlad, Gujarat, India
[b] Smt. S.M. Shah Pharmacy College, Ahmedabad-Mehmdavad Highway, On the way of Bhumapura Hanuman Temple, Aamsaran, Gujarat, 38713, India

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ABSTRACT

Isradipine (ISR), BCS Class II antihypertensive drug undergoes extensive first pass metabolism (FPM) with low bioavailability (15–24%). FPM may be avoided by formulating ISR loaded Solid Lipid Nanoparticles (SLN). Lipidic ISR-SLN get absorbed through M-Cells of peyer's patches. Preformulation study was performed. Dynasan 114 was selected as lipid. Poloxamer 407 was selected as surfactant. ISR-SLN was prepared using High Speed Homogenization-Ultrasonication method, optimized by 3^2 full factorial design. ISR-SLN was lyophilized. (1:5 = solid: cryoprotactant). Process parameters like homogenization speed, time and sonication cycle were also optimized. *In-Vitro* % Cummulative drug release(%CDR) study of ISR-SLN (dispersion & lyophilized) was performed using dialysis bag method in 0.1 N HCl + 2% tween 80 for 2 h (obtained 10% drug release) than in phosphate buffer Ph 7.4 + 2% tween 80 (Aprx. 100% drug release after 130hrs, followed higuchi model). *Ex-Vivo* %CDR was performed using chicken duodenum in same condition as *In-Vitro*. Characterization was done using zeta potential (−21.5 mv), TEM(Spherical shape and smooth surface), MPS(204 nm), %EE (90.85 ± 3.55%), XRD, DSC, FT-IR. Confocal Laser Scanning Microscopy of Rodamine B labeled ISR-SLN was performed to study uptake of ISR-SLN through M-Cells, Peyer's Patches. Stability study of 45 days shows the ISR-SLN is stable. ISR-SLN give controlled release, permeates M-Cell of Peyer's patch and are stable.

1. Introduction

ISR is having low bioavailability (15–24%) due to extensive FPM. So, by loading ISR into SLN, FPM may be avoided due to its nano size. As SLN are Lipidic in nature, they are easily absorbed via M-Cells of Peyer's Pathch of intestine. ISR is Lipidic in nature so it is efficiently loaded into SLN. Therefore, by avoiding FPM and targeting Peyer's Patch, bioavailability of ISR may be increased.

Polymeric nanoparticles made from non-biodegradable and biodegradable polymers. Advantages of these particles are site-specific targeting and controlled release of the incorporated drugs. The cytotoxicity of the polymers after internalization into cells is a crucial [1]. Furthermore, large-scale production of polymeric nanoparticles is problematic.

In the middle of the 1990s, the attention of different research groups has focused on alternative nanoparticles made from solid lipids, the so-called solid lipid nanoparticles (SLNs or lipospheres or nanospheres) [2]. SLN combines the advantages of other innovative carrier systems (e.g. physical stability, protection of incorporated labile drugs from degradation, controlled release, excellent tolerability) while at the same time minimizing the associated problems of toxicity.

Isradipine, dihydropyridine calcium-channel blocker, so that ISR does not usually decrease the heart rate [3], potent antihypertensive agent has been used in the treatment of hypertensive disorders. It is highly lipophilic (log P 2.9) [4].

The cellular lining of the gastrointestinal tract is composed of absorptive enterocytes interspersed with membranous epithelial (M) cells. M cells that cover lymphoid aggregates, known as Peyer's patches, take up nanoparticles by a combination of endocytosis or transcytosis [5]. Hence by preparing ISR-SLN, FPM may be avoided as drug and lipid are highly lipidic in nature. So they will be absorbed by lymphatic route, and it may bypass FPM, may be increasing bioavailability of Isradipine [6].

2. Materials and methods

2.1. Materials

ISR (Shasun Pharmaceuticals, Tamilnadu, India), Dynasan 114, 116, 118 (Sasol Germany), Compritol 888 ATO (Gattefose India Pvt LTD,

* Corresponding author.
E-mail address: jagrutiprajapati.ph@charusat.ac.in (J.B. Prajapati).

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Abbreviations

ISR	Isradipine
SLN	Solid Lipid Nanoparticles
ISR-SLN	Isradipine loaded Solid lipid nanoparticles
BCS	Biopharmaceutical Classification System
FPM	First Pass Metabolism
MPS	Mean Particle Size
%EE	% Entrapment Efficiency
%CDR	%Cumulative Drug Release
HCl	Hydrochloric Acid
TEM	Transmission Electron Microscopy
XRD	X-Ray Diffraction
DSC	Differential Scanning Calorimeter
FT-IR	Fourier transform infrared spectroscopy
UV-Spectrophotometer	Ultra Violet Spectrophotometer
RPM	Rotation Per Minute
CLSM	Confocal Laser Scanning Microscopy
RH	Relative Humidity
HSH	High Speed Homogenization
ANOVA	Analysis of variance

Mumbai, India), Precirol 8 ATO (Gattefose India Pvt LTD, Mumbai, India), Poloxamer 188, 407 (Hi Media Pvt LTD), Triton X (Hi Media Pvt LTD), Trehalose (Sigma Aldrich Pvt LTD), Rhodamine B (Sigma Aldrich Pvt LTD.).

2.2. Methods

2.2.1. Preformulation study

Purity and compatibility study of drug and excipients were done by Melting point determination, FTIR, DSC, XRD, Solubility and λ_{max}.

2.2.2. Preparation of ISR-SLN

High speed homogenizer and ultra-sonication method was selected for preparation of SLN because compare to other methods they are easy, less time consuming and effective. Dynasan 114 was melted at 10 °C above its melting point and ISR was dissolve in melted lipid. Poloxamer 407 was dissolved into double distilled water and heated to same temperature as of melted lipid. Transfer hot aqueous surfactant solution into ISR lipid mixture. Mixture was homogenized using high speed homogenizer at 17,500 RPM for 10 min and 2 sonication cycles were given. Dispersion was centrifuged at 8000 RPM for 10 min to remove lipid and unentrapped ISR as they settled down into centrifuge tube. Dispersion was filtered using Whatman filter (pore size 46*57). Supernatant was collected containing ISR-SLN [12].

2.2.3. Optimization of ISR-SLN

Amongst all lipids (Dynasan 114, Dynasan 116, Dynasan 118, Compritol 888 ATO, and Precirol 5 ATO), Dynasan 114 Lipid was selected based on solubility study and partition coefficient study of ISR into lipids [7]. Amongst all surfactants (Poloxamer188 and Poloxamer407), Poloxamer 407 Surfactant was selected based on minimum MPS and maximum %EE. Process parameters like sonication time, Speed of rotation of High Pressure Homogenizer (HPH), Time of rotation of HPH were optimized by trial error batch [8]. ISR-SLN was optimized by 3^2 full factorial experimental design. Formulation parameter like Drug: lipid ratio and surfactant concentration are independent variables and MPS and %Entrapment Efficiency (%EE) are dependent variables. A check point analysis was performed to confirm the role of derived polynomial equation and contour plots in predicting the responses in the preparation of solid lipid nanoparticle [9]. Differences of the theoretically computed values of dependent variables and the mean values of experimentally obtained value of dependent variables were checked by using *t*-test, which shows both values are nearer to each other as there is no significant difference as $p > 0.5$. Optimization was performed to find out the level of independent variables (X1 and X2) that would yield a maximum value of % EE and minimum value of particle size. The desirability function was used for optimization of the formulation, which is optimized using software.

Factors	Levels		
	−1	0	+1
X1 (Drug: Lipid	1:10	1:15	1:20
X2 (%Surfactant)	1%	2%	3%

2.2.4. Lyophilization of ISR-SLN

Freeze drying technique was used to improve stability of SLN and to prevent the leakage of Entrapped ISR [10]. Total solid content: Cryoprotactant (trehalose) (1:3, 1:5) were taken, optimized and selected on the basis of MPS and %EE (Table 5). Optimized Batch of ISR-SLN was freeze dried using trehalose as cryoprotactant to preserve the size and shape (1:5 = Solid content of ISR-SLN: Trehalose) [11].

2.3. Characterization of ISR-SLN

2.3.1. Particle size analysis

Particle size analysis of the formulations was performed using a Malvern zetasizer 2000MS device (Malvern Instruments, Worcestershire, UK) and laser diffraction with a beam length of 2.40 mm, R.I: 1.456 [12].

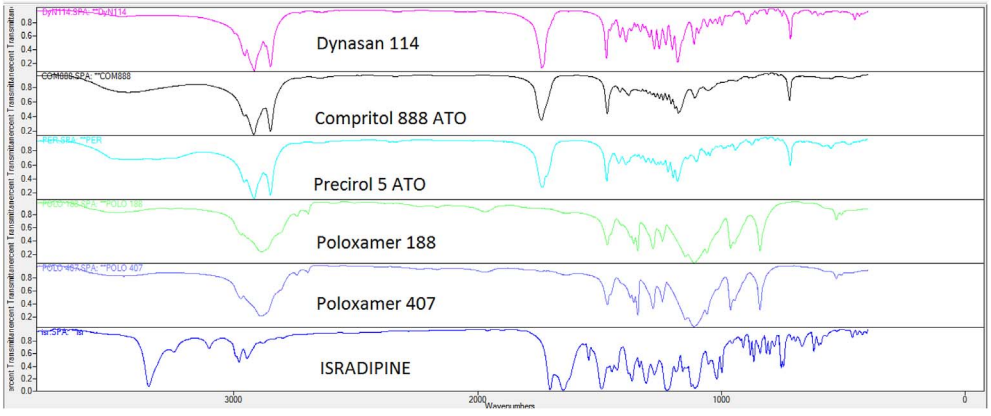

Fig. 1. FTIR spectrums of ISR and Excipientsfor preformulation study.

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