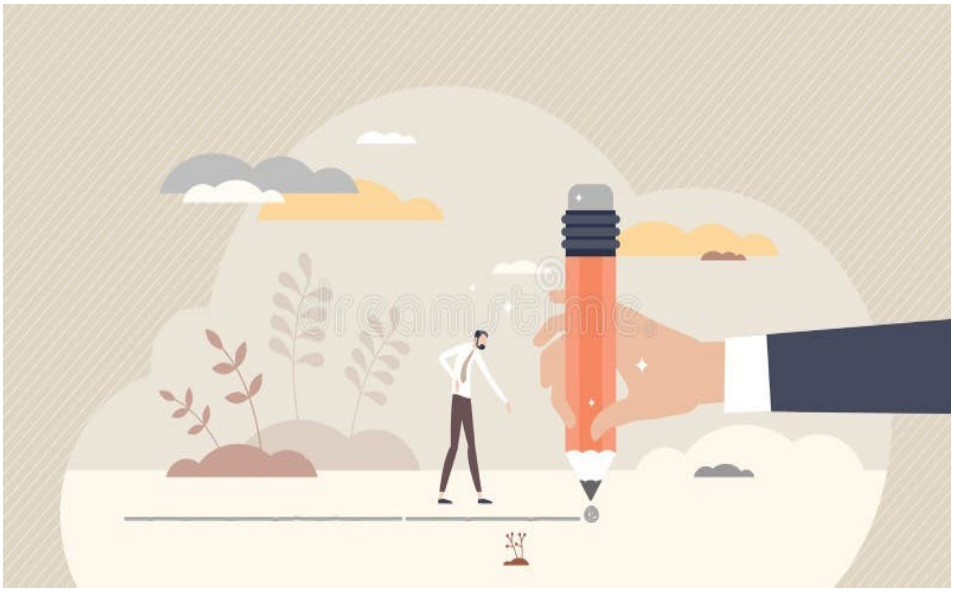

Chapter-11

Summary and conclusions

11.1. Summary:

11.1.1. Introduction:

Osteoporosis is a condition in which the bones gradually become weaker and more susceptible to fractures due to a decrease in bone mass and structural integrity. The development of osteoporosis involves a misbalance in the equilibrium between bone formation and bone resorption, which serves as a fundamental mechanism of osteoporosis. Several risks of factors for osteoporosis are glucocorticosteroids therapy, rheumatoid arthritis, smoking, alcohol consumption, age, premature menopause, etc. The osteoporosis is treated by non-pharmacological treatment such as balanced diet containing sufficient calcium and vit. D, exercise, etc. The pharmacological treatment includes many drugs and their combinations such as bisphosphonates, teriparatide, selective estrogen receptor modulators, statins, strontium ranelate etc.

Risedronate sodium (RSNa) belongs to a class of bisphosphonates and works by inhibiting bone resorption, thereby helping to maintain bone density and reduce the risk of fractures. RSNa is typically prescribed as an oral tablet for treatment of osteoporosis. The oral bioavailability of RSNa is less than 1% due to poor absorption in the GIT. After oral administration, RSNa can bind with divalent atom such as calcium, magnesium etc. and forms insoluble complexes that are poorly absorbed into the blood circulation. The half-life of the RSNa is 1.5 hrs. The side effects related to oral administration are GI disturbances, Oesophageal irritation, musculoskeletal pain, headache etc. The limitations of RSNa oral administration need to be overcome. Thus, RSNa was selected for this research work.

Atorvastatin calcium, (ATO) is a specific inhibitor of HMG-CoA reductase enzyme which block conversation of HMG-CoA to mevalonate in cholesterol synthesis. Recently, atorvastatin has reported a positive impact on bone by inhibiting osteoclast growth and encouraging osteoblast activity through increased BMP-2 protein production. The oral bioavailability of ATO is about 14% due to extensive first pass metabolism and presystemic clearance in GI mucosa. The side effects of ATO oral administration are several GI issues, muscle pain or weakness etc. The

limitations of ATO need to be overcome. Thus, ATO was selected for this research work.

The **transdermal** delivery of risedronate sodium (RSNa) and atorvastatin (ATO) has the potential to overcome the limitations associated with their oral marketed formulations. The transdermal delivery might enhance the bioavailability of the drug by avoiding first-pass metabolism (in ATO) and insoluble complex formation (in RSNa). The permeation of drugs alone through skin is limited due to the barrier property of stratum corneum layer of skin. Thus, a permeation enhancement technique is needed to enhance their permeation through skin.

Thus, in these present research work, different nanocarriers such as glycerosomes and polyelectrolyte complex nanoparticles were employed for enhancement of transdermal permeation of drugs which helps to enhance bioavailability.

Glycerosomes are novel flexible and elastic vesicular drug delivery systems for dermal and transdermal drug delivery consisting of phospholipid, cholesterol, and glycerol. Glycerosomes can improve the fluidity and deformability of vesicular bilayer which helps to improving ability of vesicles to penetrate through skin.

Polyelectrolyte complex nanoparticles (PECN) are biopolymer-based nanoparticles formed by electrostatic interaction between oppositely charged polyelectrolytes such as chitosan, heparin, alginate, pectin, hyaluronic acid, chondroitin sulfate, dextran etc. These self-assembling nanoparticles can be formed without use of organic solvent, cross-linking agents, or high energy. Various class of drugs such as hydrophilic, lipophilic, amphiphilic, and large biological molecules can be encapsulated by PECN.

The **aim of present work** was to formulate, optimize and evaluate anti-osteoporotic drugs loaded nanocarriers for the treatment of osteoporosis by enhancing permeability and bioavailability through transdermal route.

The **present work hypothesized** that the transdermal patches containing drug-loaded nanocarriers (glycerosomes and polyelectrolyte nanoparticles) for the treatment of osteoporosis will enhance the permeability of the drug through the skin membrane and deliver it to the bloodstream, which in turn will enhance the bioavailability of Risedronate and Atorvastatin.

11.1.2. Analytical techniques:

a. For ATO estimation:

UV-visible spectrophotometric method was used for the estimation of ATO in the analysis of entrapment efficiency, in vitro drug release (in PBS pH 5.5 and PBS pH 7.4) and ex vivo skin permeation study. The calibration plots were generated using UV-visible spectrometer (Shimadzu-1900) in methanol as well as PBS pH 5.5 and PBS pH 7.4 (containing 2% propylene glycol) in the range of 2-24 µg/mL concentration range. For ex-vivo study and pharmacokinetic study, HPLC method was employed using Agilent 1220 system with UV detector and C_{18} column (4.6 µm X 150 mm) at λ_{max} of 244 nm. The calibration curve was obtained in the concentration range of 50 ng/mL to 1000 ng/mL. All the techniques utilized for the estimation of ATO were accurate and precise.

b. For RSNa estimation:

UV-visible spectrophotometric method was used for the estimation of RSNa in the analysis of entrapment efficiency. The calibration plot was generated using UV-visible spectrometer (Shimadzu-1900) in distilled water in the concentration range of 5 to 50 µg/mL. For in vitro drug release study, ex-vivo skin permeation study and pharmacokinetic study, HPLC method was employed using C_{18} thermo scientific column (4.6 µm X 150 mm) and Agilent 1220 system with UV detector at 262 nm of λ_{max}. All the techniques utilized for the estimation of RSNa were accurate and precise.

11.1.3. Preformulation studies:

As part of preformulation studies, drug authenticity and compatibility with other excipients in the formulation of interest were evaluated. ATO and RSNa were authenticated based on the comparison of the melting point, FTIR spectra and DSC thermograms with reported in literature.

In case of ATO, the FTIR spectrum showed all characteristic peaks of ATO similar to reported FTIR spectrum and DSC thermogram showed endothermic peak at 161.19°C which is similar its reported melting point of 159-161°C. The drug-excipient compatibility study was performed by FTIR and the results showed that all

characteristic peaks of ATO were retained and hence, no interaction was found between ATO and excipients.

In case of RSNa, the FTIR spectrum showed all characteristic peaks of RSNa like reported FTIR spectrum and DSC thermogram showed endothermic peak at 253.2°C which is similar its reported melting point of 252-262°C. The drug-excipient compatibility study was performed by FTIR and the results showed that all characteristic peaks of RSNa were retained and hence, no interaction was found between RSNa and excipients of interested formulations.

11.1.4. ATO loaded glycerosomes:

ATO loaded glycerosomes were prepared by lipidic thin film hydration method using lipoid S-75 phospholipid. The process and formulation parameters of ATO loaded glycerosomes was screened by one factor at a time (OFAT) techniques and optimized by definitive screening design (DSD). The lipid:drug molar ratio, cholesterol:drug molar ratio, sonication amplitude and sonication cycles were selected as independent factors and vesicle size and % entrapment efficiency were selected as dependent factors. The optimized batch obtained from the overlay plot was prepared and evaluated for various physicochemical characteristics. The optimized ATO loaded glycerosomes had 159.75 d.nm, 0.350, 88.81 %, -6.08 mV, and 11.00% of vesicle size, PDI, entrapment efficiency, zeta potential and drug loading capacity. TEM image revealed the smooth spherical vesicle shape of size within 200 nm. The effect of different glycerol concentration (from 10 to 30% w/w) on physicochemical characteristics, deformability index, in vitro drug release and ex-vivo skin permeation and compared to ATO loaded liposomes (0% w/w containing glycerosomes or $AGLY_0$). The ATO loaded glycerosomes with different glycerol concentration were prepared by using optimized parameters obtained from the design. All the prepared glycerosomes were evaluated for vesicle size (VS), polydispersity index (PDI), zeta potential (ZP), entrapment efficiency (% EE), drug loading capacity (DLC) and deformability index (DI). The average VS was found in the range of 113.0 to 161.6 d.nm, 0.232 to 0.360 of PDI, -3.81 to -6.76 mV of ZP, 80.03 to 90.77 % of % EE, 10.03 to 11.18 % DLC and 12.70 to 31.74 % DI. The results of in vitro drug release study showed that increase in glycerol concentration sustained the drug release from the vesicles. From the results of ex vivo skin

permeation study, it was revealed that the increase in glycerol concentration increased the permeation of drug through skin. The glycerol concentration was optimized based on higher skin permeation, high DI and sustained in vitro drug release and based on results, 30% w/w glycerol containing ATO loaded glycerosomes ($AGLY_{30}$) was used for further studies. From the results of in vitro cell viability study, it was observed that glycerosomes had more cell viability as compared to pure drug. The in vitro cell permeability study revealed that the developed $AGLY_{30}$ was more permeable as compared to pure drug and $AGLY_0$ from cell layer. Stability study of $AGLY_0$ and $AGLY_{30}$ was conducted at 2-8°C, 25±2°C/65±5% RH and 40±2°C/75±5% RH for 90 days and evaluated for the vesicle size and % assay. Based on results, it was observed that $AGLY_{30}$ were stable at 2-8°C and 25±2°C/65±5% RH for more than 90 days.

11.1.5. RSNa loaded glycerosomes:

RSNa loaded glycerosomes were prepared by lipidic thin film hydration method using lipoid S-75 phospholipid. The process and formulation parameters of RSNa loaded glycerosomes was screened by one factor at a time (OFAT) techniques and optimized by definitive screening design (DSD) using DesignExpert V.13.0.0. The lipid:drug molar ratio, cholesterol:drug molar ratio, sonication amplitude and sonication cycles were selected as independent factors and studied significant effects on vesicle size and % entrapment efficiency. An optimized batch was prepared using composition of independent factors obtained from the overlay plot of design and evaluated for various physicochemical characteristics. The optimized ATO loaded glycerosomes had 153.8 d.nm, 0.213, 59.75 %, -18.3 mV, and 2.99 % of VS, PDI, % EE, ZP and DLC. The TEM image revealed that glycerosomes were small and uniform in size, spherical in shape and homogenously dispersed with no agglomeration. The effect of different glycerol concentration (from 10 to 30% w/w) on physicochemical characteristics, deformability index, in vitro drug release and ex-vivo skin permeation and was compared to RSNa loaded liposomes (0% w/w containing glycerosomes or $RGLY_0$). The RSNa loaded glycerosomes with different glycerol concentration were prepared by using optimized parameters obtained from the design. All the prepared glycerosomes were evaluated for vesicle size, PDI, zeta potential, entrapment efficiency, drug loading capacity and deformability index (DI). The average VS was found in the range of 97.4 to 170.2 d.nm, 0.213 to 0.426 of PDI,

-10.2 to -18.3 mV of ZP, 39.71 to 65.06 % of % EE, 2.00 to 3.27 % DLC and 11.38 to 39.95 % DI. The results of in vitro drug release study showed that increase in glycerol concentration sustained the drug release from the vesicles. From the results of ex vivo skin permeation study, it was revealed that the increase in glycerol concentration increased the permeation of drug through skin. The glycerol concentration was optimized based on higher skin permeation, high DI and sustained in vitro drug release and based on results, 30% w/w glycerol containing RSNa loaded glycerosomes ($RGLY_{30}$) was used for further studies. From the results of in vitro cell viability study, it was observed that the $RGLY_{30}$ showed more cell viability as compared to pure drug and concluded that the RSNa loaded glycerosomes is safe and non-toxic for transdermal drug delivery. From the results of cell permeability study, it was observed that the $RGLY_{30}$ showed more cell permeability than the pure drug as well as $RGLY_{0}$. The results of stability study revealed that the $RGLY_{30}$ was more stable at 2-8°C and 25±2°C/65±5% RH as compared to $RGLY_{0}$.

11.1.6. ATO loaded PECN:

The ATO loaded PECN were prepared using ionic gelation method. The chitosan was selected as cationic polyelectrolyte and chondroitin sulfate was selected as anionic polyelectrolyte for the preparation of ATO loaded PECN. The formulation and process parameters were screened by OFAT technique and optimized by Box-Behnken design (response surface methodology) using DesignExpert V.13.0.0. The Chitosan concentration (1-3 mg/mL), chitosan:chondroitin sulfate ratio (1:1 to 2:1) and pH of chitosan solution (5-7) were selected as independent variables for optimization and studied for their effect on particle size and entrapment efficiency. An optimized batch obtained from design space was prepared and evaluated for different physicochemical characteristics such as particle size (PS), polydispersity index (PDI), zeta potential (ZP), drug loading capacity (DLC), FTIR, differential scanning calorimetry (DSC) and X-ray diffraction (XRD). The results of physicochemical characterization showed 219.2 d.nm of PS, 82.68 % of % EE, 25.41 mV, and 6.67 % of DLC. The TEM image of ATO loaded PECN revealed homogenously dispersed spherical shaped nanoparticles with size less than 200 nm. The thermogram of DSC and XRD patterns of ATO loaded PECN showed disappearance of characteristic peaks indicating encapsulation of drug inside the nanoparticles. The in vitro drug release study was performed in two different pH i.e.,

pH 5.5 and pH 7.4 using dialysis bag method. The release pattern showed sustained release of drug from nanoparticles as compared to pure drug upto 48 hrs. Drug release was relatively slower at pH 5.5 as compared to pH 7.4 from nanoparticles. The ex vivo skin permeation study was performed by Franz diffusion cell using rat skin and results showed that the ATO loaded PECN permeated more amount of drug (55.23%) through skin as compared to pure drug (35.67%) in 48 hrs. The in vitro cell viability study was performed by MTT assay method and results revealed that the ATO loaded PECN showed more viability as compared to pure drug upto 24 hrs. On the basis of results, it was concluded that the PECN is safe and non-toxic for transdermal drug delivery. The results of in vitro cell permeability study revealed that the ATO loaded PECN showed more cell permeability as compared to pure drug. The stability study of ATO loaded PECN was performed at 2-8°C, 25±2°C/65% RH and 40±2°C/65±5% RH for 90 days and it was observed that ATO loaded PECN was more stable at 2-8°C and 25±2°C/65% RH for more than 90 days.

11.1.7. RSNa loaded PECN:

The RSNa loaded PECN were prepared by using ionic gelation method using chitosan as cationic polyelectrolyte and chondroitin sulfate as anionic polyelectrolyte. The formulation and process variables were screened based on minimum particle size and high entrapment efficiency by OFAT technique. The RSNa loaded PECN were optimized by Box-Behnken design (response surface methodology) using chitosan concentration (1-3 mg/mL), chitosan:chondroitin sulfate ratio (1:1 to 3:1) and pH of chitosan solution (4-6) as independent variables, and the effect of independent factors on particle size and entrapment efficiency was studied. An optimized batch was prepared using composition obtained from design space and evaluated for different physicochemical characteristics such as average PS, PDI, ZP, %EE, DLC, FTIR, DSC and XRD. The optimized RSNa loaded PECN had average PS of 171.6 d.nm, 0.280 of PDI, 21.25 mV, 61.13 % of % EE, 13.23% of DLC. The DSC thermogram and XRD patterns of RSNa loaded PECN revealed that RSNa was completely encapsulated into the nanoparticles. The TEM image of PECN showed homogenously dispersed small size spherical shaped particles. The results of in vitro drug release study showed sustained drug release from RSNa loaded PECN upto 48 hrs in both PBS pH 5.5 and PBS pH 7.4 as compared to pure drug (around 90 % of drug released within 3 hrs). Drug release from PECN was more

sustained in PBS pH 5.5 as compared to PBS pH 7.4. From the results of the ex vivo skin permeation study, it was observed that the RSNa loaded PECN permeated more amount of drug through the skin as compared to pure drug. The results showed that RSNa loaded PECN permeated 58.84% of drug, while pure drug permeated only 20.93% of drug through skin. The results of in vitro cell line study revealed that the RSNa loaded PECN showed more cell viability as compared to pure drug upto 24 hrs and hence PECN is safe to use. The RSNa loaded PECN was more permeable through the cell layer (around 94 % in 10 hrs) as compared to pure drug (around 72% in 12 hrs). The results of stability study showed that the RSNa loaded PECN was stable at 2-8°C and 25±2°C/65% RH for more than 90 days.

11.1.8. Nanocarriers incorporated transdermal patches:

The transdermal patches were prepared by solvent evaporation method. HPMC K4M was selected as polymer for preparation of patches. The various process and formulation variables were screened and optimized using OFAT technique based on physicochemical characteristics such as appearance, weight, thickness, folding endurance, tensile strength, moisture content and moisture uptake. The optimized batch of transdermal patch prepared with 2.0 % w/w of HPMC K4M and 5.0 % w/w of PEG-400 as a plasticizer at 35±5°C in hot air oven for 24 hrs drying condition showed desired physicochemical characteristics. This optimized batch was used for the preparation of nanocarriers incorporated transdermal patches.

A. ATO loaded glycerosomal transdermal patches:

The $AGLY_0$ (ATO loaded liposomes), $AGLY_{30}$ (ATO loaded glycerosomes) and ATO was incorporated into transdermal patches using solvent evaporation method and evaluated for physicochemical characteristics. All prepared transdermal patches have the desired physicochemical characteristics. The results of ex vivo skin permeation study showed that the glycerosomal patch (AGP) permeated more amount of ATO as compared to liposomal patch (ALP) and ATO loaded patch (ATP) in 72 hrs. The increasing order of transdermal flux (µg/cm^2/hr) was AGP (27.09) > ALP (21.71) > ATP (17.31).

B. RSNa loaded glycerosomal transdermal patches:

The $RGLY_0$ (RSNa loaded liposomes), $RGLY_{30}$ (RSNa loaded glycerosomes) and RSNa (control patch) was incorporated into transdermal patches using solvent evaporation method and evaluated for physicochemical characteristics. All prepared patches have the desired physicochemical characteristics. From the results of ex vivo skin permeation study, it was observed that RGP (glycerosomal patch) showed more permeation of drug through skin as compared to RLP (liposomal patch) and RTP (control patch). The transdermal flux ($\mu g/cm^2/hr$) for RGP (6.94) was found to be higher as compared to RLP (2.69) and RTP (1.93).

C. ATO-PECN incorporated transdermal patches:

The optimized ATO loaded PECN was incorporated into transdermal patch by solvent evaporation method. The ATO-PECN transdermal patch required aid of permeation enhancer to enhance permeation of drug through skin. Thus, the selection and optimization of permeation enhancer was done based on higher amount of drug permeated through skin. From the results, it was observed that 0.2 % glycerol showed more permeation of drug and hence was selected as permeation enhancer in the preparation of ATO-PECN incorporated transdermal patch. Three transdermal patches were prepared i.e., ATO-PECN incorporated transdermal patch with (APTP) or without (AWTP) glycerol and ATP as control patch and evaluated for physicochemical characteristics and ex vivo skin permeation study. All prepared patches showed desired physicochemical characteristics. From the results of ex vivo skin permeation study, it was observed that APTP showed more transdermal flux as compared to AWTP and ATP. The decreasing order of amount of drug permeated through skin was APTP (83.22%) > AWTP (65.02%) > ATP (48.73%).

D. RSNa-PECN incorporated transdermal patches:

The optimized RSNa loaded PECN was incorporated into transdermal patch by solvent evaporation method using 0.2 % glycerol as permeation enhancer in the preparation of RSNa-PECN incorporated transdermal patch. The RSNa-PECN incorporated transdermal patch with (RPTP) or without (RWTP) glycerol were prepared and compared with control patch of RSNa (RTP) and evaluated for physicochemical characteristics and ex vivo skin permeation study. All prepared

patches showed desired physicochemical characteristics. From the results of ex vivo skin permeation study, it was observed that the RPTP permeated more amount of RSNa (35.46%) through skin as compared to RWTP (69.83%) and RTP (81.26%).

The developed nanocarriers incorporated transdermal patch was evaluated for skin integrity by FTIR-ATR. From the results, negligible variation was observed in the FTIR characteristic peaks of treated skin as compared to normal skin, indicating no change in skin integrity after application of transdermal patches. The prepared glycerosomal transdermal patch and PECN incorporated patch was subjected to analysis of drug permeation using dye (FITC or Rhodamine B) through skin by fluorescence microscopy. From the results, it was observed that glycerosomal and PECN incorporated transdermal patches showed more fluorescence intensity than normal skin indicating more permeation of drug loaded nanocarriers through skin. The results of histopathology of the skin after application of transdermal patches showed minor disturbance in the upper stratum corneum layer but did not exhibit change in the dermal layer, indicating that there was no change in skin integrity after application of glycerosomes and PECN-incorporated transdermal patches.

The stability study of transdermal patch was performed at 2-8°C, 25±2°C/65±5% RH and 40±2°C/75±5%RH for 90 days and evaluated for % drug content, folding endurance, thickness, and weight for ATO loaded glycerosomal transdermal patch, ATO loaded liposomal transdermal patch, RSNa loaded glycerosomal transdermal patch, RSNa loaded liposomal transdermal patch, ATO-PECN incorporated transdermal patch, RSNa-PECN incorporated transdermal patch, ATO loaded transdermal patch and RSNa loaded transdermal patch. From the results, it was observed that ATO loaded glycerosomal transdermal patch, RSNa loaded glycerosomal transdermal patch, ATO-PECN incorporated transdermal patch, and RSNa-PECN incorporated transdermal patch were more stable at 2-8°C and 25±2°C/65±5% RH for more than 90 days.

11.1.9. In vivo pharmacokinetic and pharmacodynamic study:

Pharmacokinetic study of developed formulation was performed on Sprague-Dawley (SD) rats. Various pharmacokinetic parameters such as Cmax, Tmax, AUC, t1/2 and MRT were found out during this study by using Kinetica software. From the results of pharmacokinetic study of ATO related formulations, it was observed that the relative bioavailability of ATO loaded glycerosomal transdermal patch was enhanced by 5.03, 1.30, and 3.41 folds as compared to oral marketed formulation, ATO loaded liposomal transdermal patch (ALP) and ATO loaded patch (ATP) respectively. In case of ATO-PECN incorporated transdermal patch (APTP), the relative bioavailability was enhanced 4.76, and 3.22 folds as compared to oral marketed formulation and ATP respectively.

From the results of RSNa related formulations, it was observed that the relative bioavailability of RSNa loaded glycerosomal patches (RGP) was enhanced by 18.47, 1.57, and 7.39 folds as compared to oral marketed formulations, RSNa loaded liposomal transdermal patch (RLP) and RSNa loaded transdermal patch (RTP) respectively. In the case of the RSNa-PECN incorporated transdermal patch (RPTP), the relative bioavailability was enhanced by 12.55 and 5.02 folds as compared to the marketed formulation and RTP, respectively.

The pharmacodynamic study was performed on female Sprague-Dawley (SD) rats. The osteoporosis was induced by bilateral ovariectomy surgery and kept 90 days for induction of osteoporosis. After an induction period of 3 months, the animals were treated with marketed formulations of RSNa and ATO as well as developed formulations, i.e., drug (RSNa and ATO) loaded nanocarriers (glycerosomes and PECN) incorporated transdermal patches, for 30 days. After treatment, the animals were evaluated for antiosteoporotic activity by different parameters such as radiological analysis, bone weight, bone volume, bone density, biochemical assay (serum calcium and phosphorous level), and histopathology of bone samples. From the results of the pharmacodynamic study, it was observed that the developed formulation showed more anti-osteoporotic activity as compared to the marketed formulation.

11.2. Conclusions:

The aim of the present work was to formulate, optimise, and evaluate anti-osteoporotic drugs loaded nanocarriers for the treatment of osteoporosis by enhancing permeability and bioavailability through the transdermal route to overcome the limitations associated with the oral route. Atorvastatin (statin) and risedronate sodium (bisphosphonate) were selected drugs for the treatment of osteoporosis. The glycerosomes and polyelectrolyte complex nanoparticles (PECN) of atorvastatin and risedronate sodium were successfully prepared and optimized to have maximum entrapment efficiency and minimum size. The optimized glycerosomes and PECN of atorvastatin and risedronate sodium showed sustained release of drugs and higher permeation of drugs through the skin as compared to pure drugs. On the basis of the increased cell viability of optimized glycerosomes and PECN, it was concluded that the prepared glycerosomes are considered safe and non-toxic to use for transdermal and dermal drug delivery. The results of the stability study concluded that the prepared nanocarriers were more stable at 2-8°C and 25±2°C/65±5% RH for more than 90 days.

The prepared nanocarriers were successfully incorporated into transdermal patches and showed desired physicochemical characteristics, and an ex vivo skin permeation study demonstrated more permeation than control patch. The results of histopathology and FTIR of the skin revealed that the prepared nanocarriers incorporated transdermal patch are considered safe and non-toxic to use for transdermal application. The results of the stability study concluded that the prepared nanocarriers incorporated transdermal patches were more stable at 2-8°C and 25±2°C/65±5% RH for more than 90 days.

The optimized nanocarriers incorporated transdermal patches were evaluated for pharmacokinetic and pharmacodynamic studies. The results of the pharmacokinetic study concluded that the developed nanocarriers incorporated transdermal patches significantly enhanced the relative bioavailability of drugs as compared to orally administered marketed formulations. The results of the pharmacodynamic study revealed that the developed nanocarriers incorporated transdermal patches showed better anti-osteoporotic activity as compared to marketed formulations in a bilateral ovariectomized rat model.

The overall results of the presented work concluded that the atorvastatin and risedronate sodium-loaded prepared glycerosomes and polyelectrolyte complex nanoparticles

incorporated into the transdermal patch are promising drug delivery systems for poorly bioavailable drugs and demonstrated enhanced anti-osteoporotic activity.