Original Article

Influence of Polylactic Acid and Polycaprolactone on Dissolution Characteristics of Ansamycin-Loaded Polymeric Nanoparticles: An Unsatisfied Attempt for Drug Release Profile

Keerthi G. S. Nair, Ramaiyan Velmurugan, Sathesh Kumar Sukumaran

Department of Pharmaceutics, School of Pharmaceutical Sciences, Vels Institute of Science Technology and Advanced Studies, Chennai, Tamil Nadu, India

Abstract

Objectives: The purpose of the current examination was to establish a polymeric nanoparticle (NP) to supply Ansamycin to the central nervous system by improving blood–brain barrier permeability for bacterial meningitis, by emulsification solvent diffusion technique with numerous hydrophilic carriers. **Materials and Methods:** The polymeric NPs were prepared by emulsification solvent diffusion technique making use of Polylactic acid (PLA) as well as Polycaprolactone (PCL). Physical mixtures of drug with above-mentioned polymers were likewise prepared. The formulations were examined for Fourier-transform infrared spectroscopy and as well as differential scanning calorimetry (DSC), particle size, and also *in vitro* dissolution. Similarity factor (f2) was determined for the comparison between dissolution of pure drug and also drug polymer physical mixtures with NPs. **Results:** Phase solubility researches showed linear increase in the drug solubility with rise in carrier concentration. *In vitro* release studies disclosed that dissolution quality of Ansamycin was not satisfactory with PLA and also PCL for the release quality of the Ansamycin from the formulation. Nanoformulation of Ansamycin with PLA and also PCL displayed inadequaterate and extent of dissolution. Optimized batches of nano formulations of both the carriers were identified by the Fourier-transform infrared spectroscopy and also DSC evaluation, which suggested existence of interactions between ansamycin and carriers. **Conclusions:** PLA as well as PCL are not the appropriate polymers to serve as a carrier to deliver Ansamcyin.

Keywords: Ansamycin, *in-vitro* drug release, nanoparticles, polycaprolactone, polylactic acid

Introduction

Bacterial meningitis is a life-threatening health condition that needs timely attention and therapy. The very most common reasons of bacterial meningitis are actually *Nesseria eningitidis*, *Streptococcus pneumoniae,* and *Haemophilus influenza*. More than 1.2 million instances of bacterial meningitis are approximated to happen globally each year. Prevalence and case fatality rates for bacterial meningitis differ by location, nation, microorganism, and age. Without having therapy, the case fatality rate is able to be as high as 70%, and one in five survivors of bacterial meningitis can be left behind irreversible sequelae featuring hearing loss, neurologic impairment or loss of a limb.[1,2]

The majority of the small molecule drugs do not cross the Blood–Brain Barrier (BBB). Excessively 7000 drugs in the comprehensive medicinal chemistry database, just 5% of drugs treat the central nervous system (CNS), and these CNS active drugs treats only depression, schizophrenia, and insomnia. The average molecular mass of the CNS active drug is 357 Da. In another study, only 12% of drugs were active in the CNS, but only 1% of all drugs were active in the CNS for the diseases other than affective disorders.[3,4]

Mostly, all macromolecular drugs and also >98% of small molecule drugs cannot pass the BBB. For that reason, the BBB

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Address for correspondence: Dr. Sathesh Kumar Sukumaran, Department of Pharmaceutics, School of Pharmaceutical Sciences, Vels Institute of Science Technology and Advanced Studies, Chennai - 600 117, Tamil Nadu, India.
E-mail: sathesh2000@gmail.com

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stays a large obstacle for the delivery of drugs to the CNS. With the architectural as well as mechanistic clarification of the BBB under both physical and also pathological strategies, it is currently feasible to create delivery systems that can go across the BBB properly. Due to their helpful buildings, nanoparticles (NPs) have actually been extensively used for brain-targeted delivery.[5]

NPs are items sized in between 1 as well as 100 nm that function all at once system in regards to transportation properties. The factors for this assumption are above all connected to the opportunity of NPs multifunctionalization, paired to their capability to carry drugs, consisted of BBB-impermeant medicines. Specifically, the reasoning of utilizing NPs for brain drug delivery is that proper surface area multifunctionalization might advertise at the very same time either their targeting of the BBB or the improvement of its going across. The opportunity for BBB impermeable drugs to get to the brain, when filled in NPs, is based upon the reality that their going across of the obstacle will certainly depend entirely on the physicochemical as well as biomimetic functions of the NPs carriers as well as will certainly not depend any longer on the chemical structure of the drug, which is impeded inside the NPs.[6,7]

Polymeric NPs are products made up of a polymer matrix, including particles with a minimum of one dimension in the nanometer scale.[8,9] The use of biodegradable polymeric NPs for controlled drug delivery has shown significant therapeutic potential.[10,11] The existence of such nanofillers can considerably modify the regional characteristics and also morphology of the polymer chains in addition to the macroscopic reaction of the polymer, including its mechanical, thermal, as well as rheological properties, with which it can, penetrates the BBB to provide the integrated medicine.[12,13] In cancer, targeted polymeric NPs can be used to deliver chemotherapies to tumor cells with greater efficacy and reduced cytotoxicity on peripheral healthy tissues.[14,15] If reasonably created, polymeric NPs can have a high effect on a variety of vital drug delivery applications. Otherwise, the very same would certainly experience a variety of concerns relating to the particular elements of the formulation which would certainly be after that dealt with much less considerably.[16-18]

In the present study, an attempt have been made to fabricate polymeric NP loaded with Ansamycin making use of the polymers polylactic acid (PLA) and polycaprolactone (PCL) by emulsification solvent diffusion technique. The study clearly discloses the impact of PLA and PCL on the NP characterization of ansamycin loaded polymeric NPs.

Materials and Methods

Ansamycin was purchased from Sigma Aldrich, India. PCL, PLA and Ploxomer were gift sampled from BASF, India and dimethyl sulfoxide (DMSO) was procured from Merck Specialties Pvt. Ltd. (Mumbai, Maharashtra, India). All other chemicals used were of analytical grade.

Phase solubility analysis

Phase solubility evaluations were executed as explained by Higuchi as well as Connors.[19] An excess quantity of ansamycin was contributed to the aqueous solutions of each carrier in simulated gastric fluid having increased concentrations of individual carrier (i.e., 0.5%, 1.0%, 2.5%, as well as 5.0% w/v). Excess of ansamycin was included the above flasks including 25 ml solutions of various concentrations of carriers in simulated gastric fluid, pH 1.2, without enzymes. The flasks were secured and shaken in an environment shaker at 25°C for 24 h. The samples were filtered with Whatman filter paper (0.12 μm) and also evaluated spectrophotometrically for the dissolved drug at 274 nm. Gibb's free energy of transfer (ΔGo tr) of Ansamycin from pure media to solution of carrier was computed making use of the formula where S0/Ss is the proportion of the solubility of Ansamycin in buffer solution of polymer to that of the pure barrier media, R is gas constant in KJ/degree/mole, and also T is outright temperature level in °C.

Fabrication of ansamycin-loaded polymeric nanoparticles

An organic phase was made dissolving accurately 4 g of PLA and 2 g of Ansamycin in 10 ml of DMSO and an aqueous phase was made dissolving 0.5 g of poloxamer dissolved in 100 ml of sterile water. From that 10 ml is used as aqueous phase. Organic phase was added drop wise at the rate of 1 ml/min into the aqueous phase. The NP suspension was kept under continuous stirring at 300 rpm for 3 h to allow complete evaporation of DMSO leaving behind the colloidal suspension of Ansamycin PLA NP in the aqueous phase. The colloidal nano suspension was centrifuged at 12,000 rpm for 30 min at 40°C to get the final nano precipitate containing pellets as encapsulated Ansamycin. The pellet was washed with deionized water twice to remove the unentrapped drug from the surface of NP. NP pellets was re-dispersed in water. The same procedure was carried out with PCL. Both the NPs made of PLA and PCL were subjected to further characterization.

Characterization of ansamycin-loaded polymeric nanoparticles

Fourier transmission infrared spectroscopy analysis

The chemical integrity of the drug and polymer can be determined by Fourier transmission infrared (FTIR) analysis (SPECTRUM RX I, Perkin Elmer, USA). Approximately 2 mg of native ansamycin and the polymers PLA and PCL were mixed separately in 300–400 mg of anhydrous KBr and ground properly in a mortar pestle. The sample mixture was compressed by applying hydraulic pressure of 2000 Kg/cm^2 (Jasco MP2 mini press) for 2 min. The FTIR spectrum was obtained by scanning all samples with resolution of 2 cm^{-1} in the range of 4000–400 cm^{-1}.

Differential scanning calorimetry

The physical status of drug in the polymer and drug polymer interaction was determined by Differential Scanning Calorimetry (DSC-60, Shimadzu, Japan). The samples ansamycin NPs and native ansamycin (2–4 mg) were sealed separately in standard aluminium pans and scanned at a heating

rate of 10ºC/min over a temperature range of 50°C–350°C with continuous nitrogen gas flow of 65 mL/min.

Determination of particle size

Mean particle size was determined by using Zetasizer Nano ZS particle analyzer (Malvern Panalytical, UK) based on dynamic light scattering technique. Measurement of Zeta potential by Zetasizer Nano ZS particle analyzer (Malvern Panalytical, UK) based on electrostatic or charge repulsion/attraction between particles. Briefly sample solution of Ansamycin NPs made of both the polymers PLA and PCL were placed in polystyrene cuvettes and particle size was measured.

Determination of drug content

Drug content was figured out by liquifying precisely evaluated amount of formulation in 0.1 N NaOH.[20] After that, proper dilutions were made as well as samples were determined spectrophotometrically at 271 nm as well as the drug material was determined.

In-vitro drug release study

Drug release studies were executed thrice for statistical significance on a dissolution test apparatus at 37°C ± 0.5°C using USP apparatus, 1 in 900 ml of SGF (USP XXIII, pH 1.2) for 1 h.[21] The rotational speed of the basket was set as 100 rpm. Dissolution researches were done on pure drug (10 mg) as well as the NP consisting of an equal quantity of the drug. Aliquots (5 ml each) were taken out at established time periods for 1 h and also sink condition was preserved. The samples were evaluated spectrophotometrically (design no. UV 1700 PC, Shimadzu Corporation, Tokyo, Japan) at 274 nm.

Data analysis

Sampling time representing the quantity of drug released in that time (e.g., DP20 min) was calculated. Similarity factor *f* 2 was determined for contrast of *in vitro* dissolution of strong dispersions with pure drug as well as physical blend. A model-independent mathematical method suggested by Moore as well as Flanner for determining a similarity factor *f* 2 was made use of to contrast dissolution profiles of various samples.[22] The *f* 2 value was determined utilizing the listed below formula:

Where,

Rt = % drug dissolved at each time point from reference,

Tt = % drug dissolved at each time point from test product, and

n = number of observations.

A value of 100% for the similarity factor (*f*2) suggests that the test and reference profiles are identical. Values between 50 and 100 indicate that the dissolution profiles are similar, while lower *f* 2 values imply an increase in dissimilarity between release profiles.[22]

Results

Phase solubility analysis

Solubility of Ansamycin in SGF, pH 1.2, without enzymes was observed to be 7.82 µg/ml, showing that ansamycin is significantly inadequately soluble in SGF, pH 1.2, without enzymes. Different criteria calculated from the phase solubility research studies [Table 1] exposed linear increases in drug solubility with enhanced carrier levels, with R2 values of 0.9992, and also 0.9995 for PLA and PCL as carriers, specifically.

Infrared spectroscopy

FTIR analysis is used to study the interactions between ansamycin and the polymers PLA and PCL used in the formulation. The infrared spectra of ansamycin, the polymers used, their physical mixture, and the formulation of the same were shown. Ansamycin procured their entire characteristic peak in the physical mixture. That is significant peak 2400–3100 were retained in the physical mixture. Peak at 3055, i.e., O-H stretching was prominent in Ansamycin along with the physical mixture. In the fingerprint region of Ansamycin, the characteristic band at 1578 C-O stretching, 1550-1468 C-C stretching, and 1243C-N stretching were retained in the physical mixture. On the basis of FTIR spectra investigation, no chemical interactions were observed between drug and polymer. PLA and PCL are all aliphatic polyesters with similar structures. The C,O, C–O–C, and C–C peaks were clearly visible at 1754, 1175, and 1200 cm^{1}.

Differential scanning calorimetry

The thermal behavior of ansamycin was investigated by DSC. The pure ansamycin shows a sharp endothermic peak that corresponds to melting point at 170°C, and the same was represented in Figures 1 and 2.

Determination of particle size

Mean particle size was identified by utilizing Zetasizer Nano ZS particle analyzer (Malvern Panalytical, UK) based upon

Table 1: Solubility parameters of Ansamycin

Carrier	Slope	R^2
PLA	3.617×10^{-4}	0.9992
PCL	23.24×10^{-4}	0.9995

PLA: Polylactic acid, PCL: Polycaprolactone

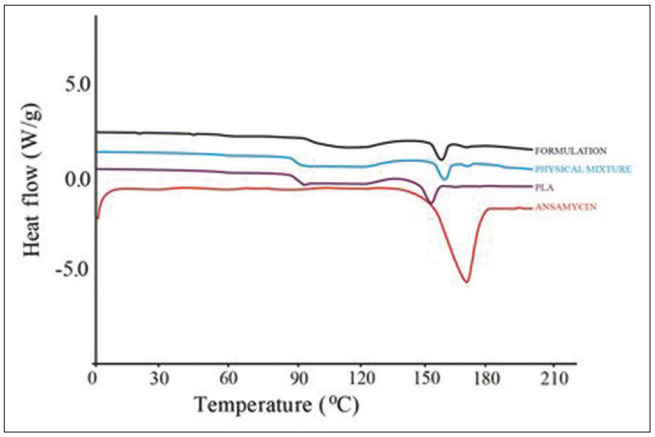


Figure 1: Differential scanning calorimetry thermogram of Ansamycin, polylactic acid, physical mixture and formulation

EQ1

dynamic light scattering strategy and also the mean particle size varies from 100 to 200 nm as well as an extra peak was likewise discovered which might result from the physical interaction between the drug candidate and also the polymers utilized, well stood for in Figure 3. The importance of zeta potential value is that its value can be associated with the brief and also long-term stability. The zeta potential value of -11 to -20 mV gotten might have a tendency to coagulate or flocculate, potentially causing poor physical stability.

Drug content determination

The drug material values computed making use of linear equation in the NPs prepared from PLA as well as PCL are summed up in Table 2. In all the proportions of drug: polymer, the drug material was >99%.

In vitro dissolution study

The results from dissolution research exposed an inadequate dissolution rate of Ansamycin NPs developed from both the polymers (PLA and also PCL). The cumulative amount of drug liquefied from pure drug and as well as NPs was researched. The worth of collective drug release was significantly trivial from the pure drug to NP. Collective drug release from NPs suggested inadequate dissolution rate.

Discussion

Phase solubility evaluations were executed as explained by Higuchi as well as Connors.[23] Hydrophilic carriers are understood to interact with drug molecules mostly by electrostatic pressures as well as periodically by various other kinds of pressures such as hydrogen bonds.[24] Table 1 illustrates the numerous criteria gotten from phase solubility research studies. Values of slope acquired for both the carriers (PLA and also PCL) were much <1.0, showing fast boost in solubility of Ansamycin. In addition, as displayed in Table 3, the Gibb's free energy values, ΔG^{o} tr, were negative, suggesting spontaneous solubilization procedure of Ansamycin in both the carriers (PLA and also PCL).

Formulation of Ansamycin was carried out with solvent evaporation technique[25] making use of PLA and PCL and the same was subjected to characterized to particle size, zeta potential and drug release status. The size range and zeta potential was not up to the mark and that may be due to incompatibility encountered between the drug and polymer and may be even due to improper processing conditions in fabricating NPs.

Various proportions of polymers were used in fabricating the Ansamycin NP and in all the proportions of drug and polymer, the drug material was >99%. Tables 4 and 5 reveal the *in vitro* drug release account of Ansamycin, its physical blend as well as formulations utilizing PLA as well as PCL as polymers. As the drug to polymer proportion was boosted, inadequate dissolution rate was observed. It could be as a result of a complex formation between the drug as well as polymer.[21] Physical mixture likewise reveals an obstacle in the dissolution rate of drug. The potential factor for an inadequate dissolution rate with both the polymers made use of may be because of the tight complexation of Ansamycin by hydrophilic polymer.[21] However, an initial burst release in the delivery system made of both PLA and PCL were observed, and it could be accounted for any free or surface-bound drug.

Tables 6 as well as 7 program *f* 2 values for *in vitro* dissolution of pure drug and nanoparticle as well as physical mixture and

Table 2: Drug content data

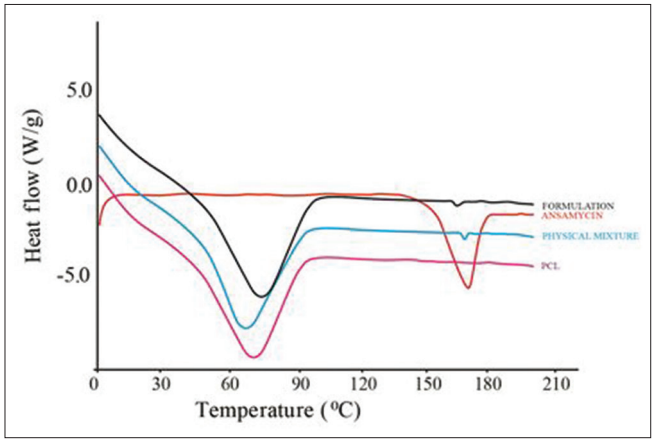
Formulations*	Percentage drug content±SD**
NP PLA 1:1	99.89±1.26
NP PLA 1:2	99.92±1.45
NP PCL 1:1	99.23±1.88
NP PCL 1:2	99.35±1.23

*NP PLA is Ansamycin nanoparticle made of PLA, NP PCL is Ansamycin nanoparticle made of PCL, **The trials were in triplicate. NP: Nanoparticle, PLA: Polylactic acid, PCL: Polycaprolactone

Table 3: Values of Gibb's free energy

Concentration of carrier (% W/V)	ΔGotr (KJ/mole) for water soluble carriers	
	PLA	PCL
0.5	−278.82	−268.48
2	−189.8	−352.66
2.5	−238.62	−684.28

PLA: Polylactic acid, PCL: Polycaprolactone



EQ1 **Figure 2:** Differential scanning calorimetry thermogram of Ansamycin, polycaprolactone, physical mixture and formulation

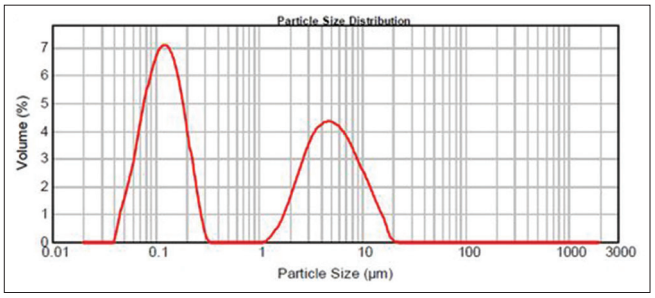


Figure 3: Particle size of Ansamycin polymeric nanoparticle EQ1

Table 4: Dissolution data of formulations with polylactic acid (drug to carrier ratios of 1:1 and 1:2)

Time (min)	Ansamycin (% drug release)	Physical mixture 1:1 (% drug release)	Physical mixture 1: (% drug release)	Nanoparticle 1: (% drug release)	Nanoparticle 1: (% drug release)
0	0.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0
10	23.03±1.04	14.34±1.64	5.86±0.97	13.03±1.04	9.91±3.79
20	32.33±3.65	17.59±1.71	8.08±1.09	14.33±3.65	11.11±3.83
30	41.03±2.33	20.36±1.77	9.36±1.39	15.03±2.33	12.71±4.46
40	44.69±3.17	22.27±1.99	10.22±1.76	17.69±3.17	13.78±4.34
50	52.20±3.21	24.86±2.15	11.35±1.69	18.20±3.21	15.97±4.24
60	89.85±3.29	27.37±2.11	12.54±0.77	19.85±3.29	16.34±1.15

Table 5: Dissolution data of formulations with polycaprolactone (drug to carrier ratios of 1:1 and 1:2)

Time (min)	Ansamycin (% drug release)	Physical mixture 1:1 (% drug release)	Physical mixture 1:2 (% drug release)	Nanoparticle 1:1 (% drug release)	Nanoparticle 1:2 (% drug release)
0	0.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0
10	16.47±4.84	3.49±1.36	2.44±1.51	3.44±1.59	2.36±0.43
20	21.82±2.61	5.45±1.24	4.12±1.31	4.77±1.15	3.13±0.53
30	25.93±2.37	6.35±1.33	5.03±1.45	5.73±4.38	3.58±1.37
40	29.86±3.26	7.17±1.26	5.76±1.36	5.76±3.11	3.74±1.13
50	48.10±2.30	8.12±1.53	6.41±2.23	6.86±4.21	4.04±1.21
60	91.12±2.46	8.89±0.25	7.15±0.39	7.51±2.30	4.20±0.15

Table 6: Comparison of *f*2 value between dissolution of pure drug and nanoparticle

Comparison between pure drug and nanoparticle	NP PLA 1:1	NP PLA 1:2	NP PCL 1:1	NP PCL 1:2
*f*2	56.97	69.18	59.86	62.35

NP: Nanoparticle, PLA: Polylactic acid, PCL: Polycaprolactone

Table 7: Comparison of *f*2 value between dissolution of physical mixture and nanoparticle

Comparison between physical mixture and nanoparticle	NP PLA 1:1	NP PLA 1:2	NP PCL 1:1	NP PCL 1:2
*f*2	59.50	62.91	54.72	61.59

NP: Nanoparticle, PLA: Polylactic acid, PCL: Polycaprolactone

nanoparticle. In all the instances, f_2 values are discovered to be >50, which clarify an inadequate dissolution account of NPs when contrasted to pure drug along with physical combinations.

In the FTIR spectrum of their formulation of both PLA and PCL, the characteristic absorption peaks of ansamycin is almost masked by that of the polymers PLA and PLC. It can be seen that the spectra of PLA and PCL reappear in the spectra of physical mixture and nanoformulation. This indicates that functional groups in nanoformulation of polymer and the drug candidate are a combination of constituent components. In addition, the spectra of nanoformulation had no new peaks. Therefore, it can be concluded that the nanoformulation produced was the result of the blend of PLA, PCL, and drug candidate is formed only by the chemical interaction between them. It can also be seen from the FTIR spectrum [Figures 4 and 5] which shows both components of PLA and PCL.

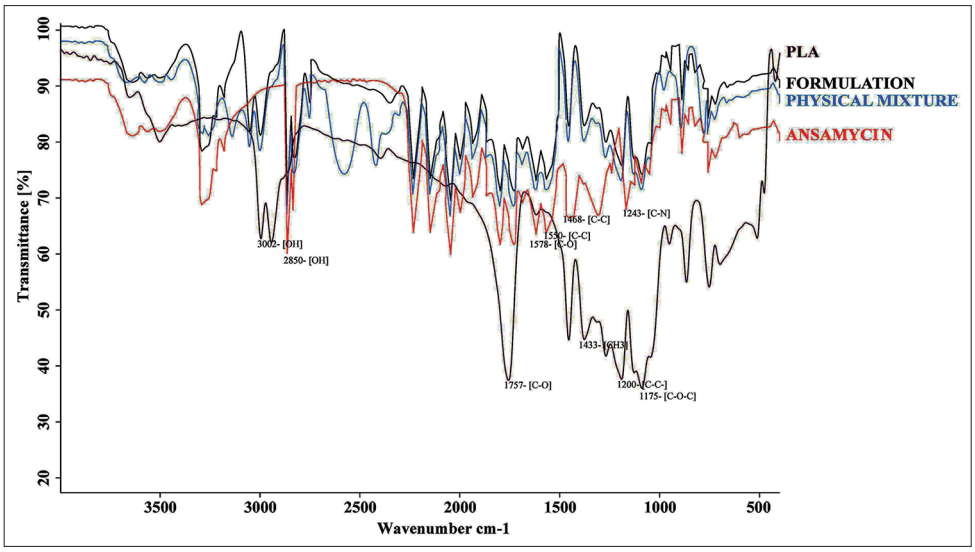
The DSC Thermogram of Ansamycin was compared with DSC thermogram of mixture of Ansamycin and polymers used in the formulation and there should be no interference in the peak of drug and polymers. The DSC of the mixture of drug sample and polymers was found to be within the specified range. Hence, there is no interaction between the drug sample and the polymers likely to be used in the formulation and hence can be used in the formulation.

Henceforth, with formulation and characterization of ansamycin NPs, data obtained were unsatisfactory, and it is that for every researcher, to come up with an innovation in formulation and technology transfer, choosing the study ingredients that are compatible to each other is the first important factor.

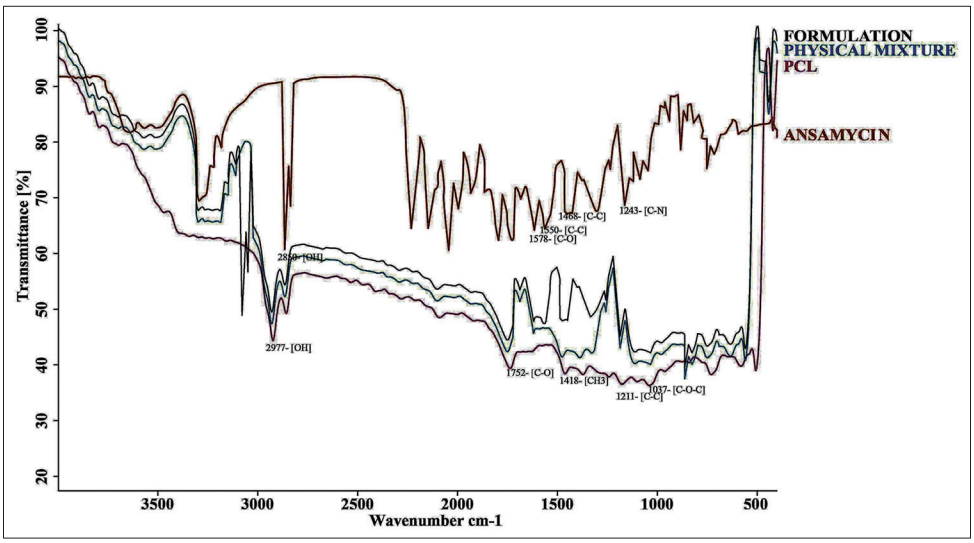
An attempt was given in fabricating ansamycin with poly lactic-co-glycolic acid (PLGA) as a polymer and observed for no interactions with respect to DSC and FTIR. Dissolution profile even showed a satisfactory drug release rate of 38% at 6 h, 52% at 12 h as well as 94% at 36 h. A slow and sustained drug release was observed with the ansamycin NPs made of PLGA.

Conclusions

Ansamycin NP was prepared with PLA as well as PCL by the emulsification solvent diffusion method. *In vitro* drug release accounts from NPs were much better than that of the physical mixes and also pure drug. FTIR evaluation suggested interaction among ansamycin as well as polymers.



EQ1 **Figure 4:** Fourier transmission infrared spectra of ansamycin, polylactic acid, physical mixture and formulation



EQ1 **Figure 5:** Fourier transmission infrared spectra of ansamycin, polycaprolactone, physical mixture and formulation

The outcomes of DSC research study exposed decline in drug crystallinity in fabricated NPs. The optimum drug release attained from NP was 16% (PLA), which is not enough total up to put in restorative prospective. Hence, it calls for additional tests in NP strategies and also polymers to bring the dissolution account in the variety of much better launch. However, NP strategy enhanced the phase solubility of the drug candidate. Therefore, NP by emulsification solvent diffusion strategy can be made use of to boost the dissolution of also extremely improperly soluble drug of course IV. It's attainable to downsize the possibility of such undesirable and also costly circumstances by allying understanding with recognition of excipient sensitivity and also of the deposits that they will certainly include and also furthermore their constraints to be taken advantage of in the solutions. An also handed selection of excipients as well as their usage constraints can omit or limit deposits promoting negative outcomes.

Perhaps, it might be a topic for a future initiative. In recap, information of drug-excipient interactions, finest excipient, and also similarly the right quantity of the excipient may be a needed need to the innovation of dosage kinds that are constant and also of fantastic top quality. It is really hoped that this research study provides some viewpoint of this necessary area of pharmaceutical development.

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Conflicts of interest

There are no conflicts of interest.

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