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Pegylated PPI Dendrimer Cored with Ethylene Diamine for Prolonged Release of Prednisolone

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Abstract

The present study aims at exploring and developing the use of PEGylated poly(propylene imine) dendritic scaffold for the delivery of an antileukemic drug, Prednisolone. For this study, PEGylated poly(propylene imine) dendritic scaffold was synthesized and loaded with Prednisolone. Various physicochemical and physiological parameters IR, NMR, SEM, drug release, hemolytic toxicity, DSC and drug entrapment of both PEGylated and non-PEGylated systems were determined and compared. Drug-loading capacity was found to have increased with the PEGylation and reduced their hemolytic toxicity and drug release rate, so prolonged delivery of Prednisolone were found suitable with these systems.

Keywords: PEGylated dendrimers; Prednisolone; Prolonged release

Introduction

A novel type of polymeric material is dendrimer. It is also known as arborols [1] or molecular trees [2] cascade or [3] or starburst, or polymers. Because of their unique structure, high degree of control over molecular weight and the shape they attract the increasing attention of all that has led to the synthesis of unimolecular micelles [4]. In recent years by molecular simulation, dendrimers have been synthesized on a relatively large scale and characterized experimentally [5]. The possible applications of the poly(propylene imine) dendrimers are generally based on the following characteristics: larger number of readily accessible end groups; regular size and shape; either nitrile or amine; possibility of end group modification in order to tailor properties such as reactivity, toxicity, solubility, stability, temperature, polyelectrolyte character, glass transition and possibility of encapsulating guest molecules [6].

PEG is considered to be capable and biocompatible of coexistence with living tissue or organisms without causing harm [7]. It has been shown that proteins decreases their immunogenicity and increases their circulation time by covalent attachment of poly ethylene glycol [8]. Polymer micelles and liposomes suppress their interaction with plasma proteins and prolong their blood elimination half-life by grafted to their surface [9]. Poly(ethylene glycol) grafts are attractive compounds as drug carriers in *in vivo* on the basis of these findings. Due to their hydrophilic shell consisting of poly(ethylene glycol) grafts such molecules are expected to encapsulate drugs in their dendrimer moiety and reveal biocompatibility [10].

The current study aims at developing and exploring the use of PEGylated newer PPI dendrimers for delivery of anti-leukemic drug, Prednisolone. Prednisolone was selected for incorporation into PEGylated ethylene diamine - PPI dendrimers based on its anti-leukemic activity, short biological half-life and solubility characteristics. PEGylation of PPI dendrimers establishes suitability of PEGylated dendrimer as a drug delivery system for Prednisolone. Through i.v. route it was observed that the hemolytic study of this delivery system could be safely administered. By delivering the drug at a controlled rate for a prolonged period of time we expect that this approach will improve the management of drug therapy in leukemic patients.

Materials and Methods

Materials

PEG_{4000}, Reney Nickel (Sigma, Germany), Raney Nickel (Merck, India), triethylamine, dioxan, ethylene diamine, N, N dicy-clohexyl carbodiimide (DCC), Cellulose dialysis bag (MWCO 12-14 Kda, Himedia, India), 4 dimethyl amino pyridine (SD - fine chemicals, India), Prednisolone was a benevolent gift from Shasun pharmaceuticals, Chennai, India.

Synthesis of 5.0G PPI dendrimers

EDA-PPI dendrimers were synthesized by the previously reported and established procedure [11] The half generation EDA-dendrimer-(CN)4*n* (where *n* is generation of reaction or reaction cycle) was synthesized by double Michael addiction reaction between acrylonitrile (2.5 molar times per terminal NH_2 group of core amine moiety) and aqueous solution of ethylenediamine or previous full generation dendrimers. After the initial exothermic phase, the reaction mixture was heated at 80°C for 1 h to complete the addiction reaction. The excess of acrylonitrile was then removed by vacuum distillation (16 mbar, bath temperature 40°C). The full generation EDA-dendrimer-(NH2)4*n* was obtained by hydrogenation in methanol at 40 atm hydrogen pressures and 70°C for 1 h with Reney Nickel (pretreated with hydroxide and water) as catalyst. The reaction mixture was cooled, filtered and the solvent was evaporated under reduced pressure. The product was then dried under vacuum. EDA-PPI dendrimers up to 5.0G were prepared by repetition of all the above steps consecutively, with increasing quantity of acrylonitrile. The scheme of the synthesis is shown in Figure 1.

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Synthesis of PEGylated 5.0G PPI dendrimers

To a solution of 5G EDA-PPI dendrimer (0.01 mmol) in dimethyl sulfoxide (DMSO) (10 ml), PEG 4000 (0.32 mmol) in DMSO (10 ml) and N,N-dicyclohexyl carbodiimide (DCC) (0.32 mmol) in DMSO (10 ml) were added and the solution was stirred for 5 days at room temperature. The product was precipitated by addition of water, filtered and dialyzed (MWCO 12-14 Kda, Himedia, India) against double distilled water for 24 h to remove free PEG 4000, DCC and partially PEGylated dendrimers followed by lyophilization (Heto drywinner, Germany). The synthesis was shown in Figure 2.

Drug loading in PEGylated dendrimers

The known molar concentrations (1:0.5, 1:1, 1:2) of PEGylated-PPI dendrimers were dissolved separately in methanol and mixed with methanolic solution of Prednisolone. The mixed solutions were incubated with slow magnetic stirring (50 rpm) using Teflon beads for 24 h. These solutions were twice dialyzed in cellulose dialysis bag (MWCO 1000 Da Sigma, Germany) against double distilled water

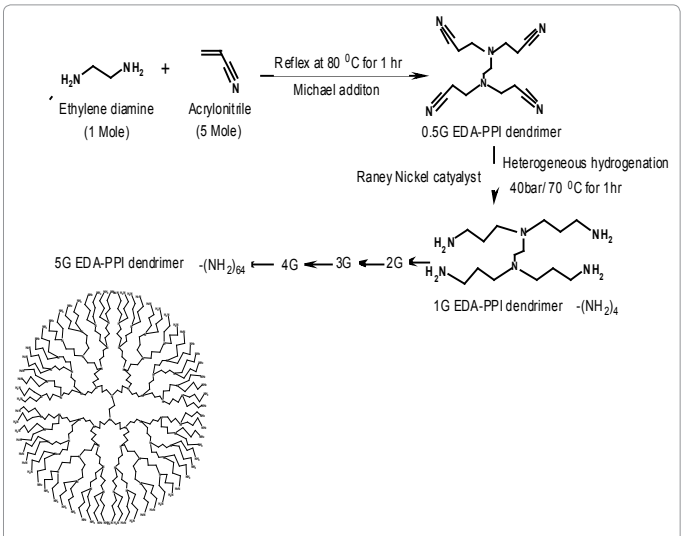

Figure 1: Schematic diagram for synthesis of PPI-5G dendrimer.

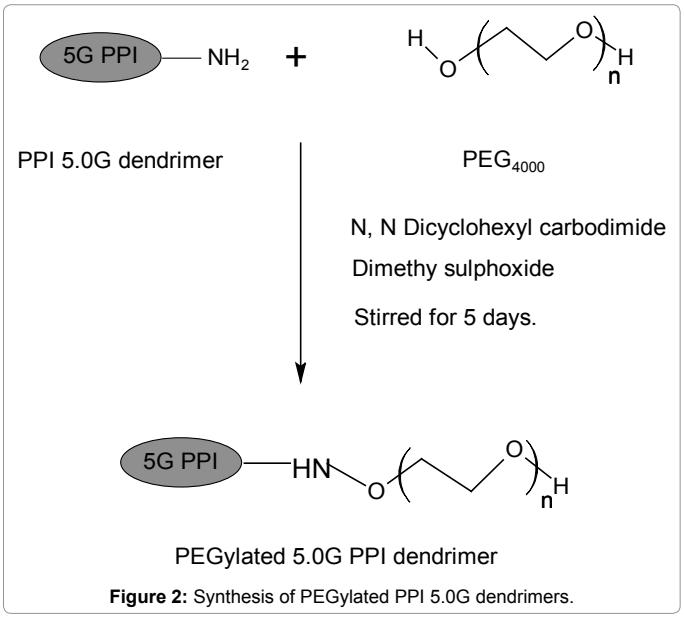

Figure 2: Synthesis of PEGylated PPI 5.0G dendrimers.

under sink conditions for 10 min to remove free drug from the formulations, which was then estimated spectrophotometrically (λmax 248 nm) (UV-1601, Shimadzu, Japan) to determine indirectly the amount of drug loaded within the system. The dialyzed formulations were lyophilized and used for further characterization.

Morphology of the dendrimers

Morphology of drug loaded dendrimers was observed by scanning electron microscope. A small amount of nanoparticles sample has been spread on a metal stub. The stub was then coated with conductive gold by Hitachi 1010 ion sputter and was examined under Hitachi 3000N scanning electron microscope (JSM 5610 LV SEM, JEOL, Japan) chamber. The image was snapped at an acceleration voltage of 20 kV with a chamber pressure of 0.6 mmHg.

Particle size and polydispersity index determination

Drug loaded dendrimers size was determined by using a Zetasizer 300 HS (Malvern instruments UK). Samples were diluted with distilled water (2 µg/ml) and measured at a temperature of 25°C. The diameter was calculated from the autocorrelation function of intensity of light scattered from nanoparticles. The Particles measured are in triplicate. The polydispersity index (PDI) was calculated for dispersion homogeneity and ranges from 0 to 1. The value close to 0 indicated a homogeneous dispersion and greater than 0.3 indicate high heterogeneity [12].

FT-IR and NMR spectroscopy

FTIR spectra of plain dendrimer, PEGylated dendrimer, respective drug and drug loaded dendrimers were determined by using Perkin Elmer RXI model. The pellets were prepared by gently mixing of 1 mg sample with 200 mg potassium bromide at high compaction pressure. The pellets thus prepared were scanned at resolution of 4 cm^{-1} from 450 to 4000 cm^{-1}. The Plain and PEGylated dendrimers were analysed by using Bruker DRX-300, NMR spectroscopy. The dendrimers were solubilised in D_2O using methanol as co solvent and analysed at 300 MHz.

In vitro release of drug from PEGylated dendrimers

Drug releases from known amount of drug loaded PEGylated dendrimers were determined using a modified dissolution method. The medium comprised of a 0.05 mol phosphate buffer solution (PBS) (pH 7.4). The dialysis bags were filled with a known mass of plain drug and drug loaded PEGylated dendritic architectures (MWCO 1000 Da) separately and the dialysis bags were placed in 50 ml of PBS (pH 7.4) at 37°C with slow magnetic stirring under sink conditions. Aliquots of 1 ml were withdrawn from the external solution and replaced with the same volume of fresh PBS. The drug concentration was detected in a spectrophotometer at 248 nm [13].

Release kinetic study

In order to understand the mechanism and kinetics of drug release, the results of the in vitro drug release study were fitted to various kinetics equations like zero order (cumulative% drug release vs. time), First order (log cumulative% drug retaining time), and Higuchi matrix (cumulative %drug release vs. square root of time), In order define a model which will represent a better fit for the formulation, drug release data were further analysed by Peppas equation, $Mt/M\infty = Ktn$, Where Mt is the amount of drug released at time " t " and $M\infty$ is the amount released at ∞, $Mt/M\infty$ is the fraction of drug released at time "t" k is the kinetic constant, and n is the diffusional exponent, a measure of the primary mechanism of drug release. R^2 values were calculated for the linear curves obtained by regression analysis of the plots [14].

Stability studies of drug loaded PEGylated dendrimers

PEGylated dendritic system loaded with Prednisolone was exposed to conditions of temperature and light for 4 weeks. The formulation was taken in different vials and stored in dark (amber color vials) and in light (colorless vials) at, room temperature (40 ± 2°C) in thermostatically controlled oven for a period of 4 weeks. The samples were analyzed every week for any color change, drug content and drug release. The data obtained were used for the analysis of any physical and chemical degradation, the required storage conditions and the precautions required for storage. The samples were initially clear and transparent at 0°C. The loss of drug from the formulation was ascertained after storage conditions. The known amount of formulation was kept in benzoylated cellulose tubing (Sigma, USA) and dialyzed across the tubing. The external medium (10 ml methanol) was monitored for the content of the drugs spectrophotometrically. The percentage increase in drug release from the formulation was used to analyze the effects of conditions of storage on the formulations [15].

Determination of pharmacokinetic parameters in animal model

For the pharmacokinetic study the albino rats were grouped in to four and each group containing six animals. Each group was considered for individual treatment respectively. The response of the formulations in rats was evaluated by determining plasma profiles after single dose administration of 100 µg of respective drug and formulations by intravenous route. Parallel groups received subsequently with the other formulation and free drug of the same. With frequent interval the blood sample was collected and availability of drug content in plasma analysed to know the AUC, AUMC, $t_{1/2}$, Cmax, Tmax and MRT by using UV-spectroscopy (at 248 nm) for drug and its formulations.

Antileukemic activity

The in vivo studies were performed in male hybrid BDF_1 mice. The animals were divided into five groups containing each of six animals. Group-I received plain Prednisolone, group-II received prednisolone loaded PEGylated dendrimers, and group III kept as negative control. The antileukemic activity was studied on ascitic form of myelogenous AML-193 cell lines, with transplantation dose of 1×10^5 tumor cells/mouse, on day 0, intraperitoneally (i. p.). Plain prednisolone, Imatinib and drug loaded PEGylated polypropyleneimine dendrimer were introduced intraperitoneally, once a day, on day 1, day 4 and day 8 after the tumor transplant. The antileukemic activity was assessed by use of the criterion T/C%, where T was the mean survival time (MST, days) of the drug treated mice, bearing AML-193 myelogenous leukemia cell lines, C - the mean survival time (MST, days) of untreated control animals, bearing the same leukemia cell lines [16].

Statistical analysis

The results are expressed as mean ± standard deviation (S.D.) (n = 3) and statistical analysis was performed with SPSS 10.1 for Windows® (SPSS®, Chicago, USA). The differences in antileukemic activity between the Prednisolone loading in PEGylated PPI dendrimers and pure prednisolone were observed by pair-wise comparisons using unpaired t test performed in GraphPad InStat version 3.00.

Results and Discussion

Synthesis and characterization PEGylated dendrimers

FTIR and NMR spectroscopy: PPI 5.0G dendrimers were synthesized with slight modification of the procedure reported by kumar et al. [7] using ethylenediamine as initiator core. Synthesis of 0.5G PPI was confirmed by IR peaks, mainly of nitrile at 2248 cm^{-1}. All the nitrile terminal 0.5G PPI got converted to (NH2)4, which was confirmed by IR of PPI 1.0G that exhibited major peak at 3284.78 cm^{-1} for amine (N-H stretch). Likewise, IR peaks also confirmed the synthesis of PPI 5.0G dendrimers. The main peaks are of C-C bend (1115.21 cm^{-1}); C-N stretch (1243.44 cm^{-1}, 1374.50 cm^{-1}); C-H bend (1477 cm^{-1}); N-H deflection of amine (1665.40 cm^{-1}) and primary amine at 3410 cm^{-1}(N-H stretch), confirming that nitrile terminal groups of dendrimer were converted to amine terminals. The results matched with the reported synthesis of PPI dendrimers. The synthesized dendrimers were PEGylated using DCC and PEG 4000. IR and NMR data proved the synthesis of PEGylated dendrimers. The IR spectrum of PEGylated PPI 5.0G dendrimer exhibited major peak of N-H stretch of amide at 3324.70 cm^{-1}. An important IR peak at 1242.75 cm^{-1} of ether linkage (C-O) appears in the spectrum of PEGylated dendrimers. C-O stretch of amide group has been found near 1624.29 cm^{-1}. The important peak of C-N stretch of amide also appears at 2925.43 cm^{-1}**.** NMR spectrum and shifts of PEGylated dendrimers as compared to that of simple dendrimers proved PEGylation. There was increase in integral value for the shift of secondary -CH2 groups on PEGylation. This is due to the increase in number of secondary -CH2 groups in PEG that are linked on PEGylation. Similarly, strong peak of ether linkage appears at 3.507 ppm due to the presence of ether linkages in PEG in high amount, remaining free amines $-CH_2-NH_2$ appears at3.341-3.410 ppm. The characteristic peak of amide linkage appeared near 2.504 ppm and 2.496 ppm for carbonyl $-CH_2C=O$ in NMR spectrum of PEGylated dendrimers.

Drug loading in to the PEGylated dendrimers

The known molar concentrations (1:0.5, 1:1, 1:2) of PEGylated-PPI dendrimers and drug Prednisolone, was used to load the drug in to PEGylated dendrimer system for getting optimized formulation. Non-covalent interactions between Prednisolone and PEGylated PPI 5.0G dendrimers, such as hydrophobic interaction and hydrogen bonding, contributed to the physical binding of drug molecules inside dendritic micelles and surface PEG layers. The percentage loading of both the drugs in PEGylated PPI 5.0G dendrimers was significantly increased in 1:1 ratio of dendrimer: drug for the formulation (p value 0.0001, extremely significant) compared to 1:0.5 and 1:2 molar concentration of both the drugs respectively. PEGylation increases the Prednisolone loading capacity of the PPI 5.0G dendrimers due to more interaction of drug and PEG at the peripheral portions of dendrimers. Prednisolone entrapment in PEGylated dendrimers increased significantly due to more sealing of dendrimeric structure by PEG at the peripheral portions of dendrimers as coat, which prevented drug release by enhancing complexation probably by increasing steric hindrance over dendrimer periphery [17,18].

Number of moles of the drug entrapped in 1 mol of PEGylated dendritic architecture was found to be in 1:1 ratio of dendrimers and drug is suitable as 89.20 ± 0.2 mol for Prednisolone as compared to 7.28 ± 1.9 mol in 1:0.5 molar concentration and 48.4 ± 1.2 molar concentrations in 1:2 ratio. If the drug entrapment is more than the required quantity leads to toxic to the host, increase in size leades to internal pressure were by leakage of drug from the system may happen. So the study considered to take up only the 1:1 ratio molar concentration followed in the preparation. The entrapment efficiency of PEGylated formulation of drug shown in Table 1.

Morphology of the dendrimers

The morphology and surface character of Prednisolone dendrimers were observed by SEM. The scanning electron micrographs of

PEGylated dendrimers and both Prednisolone dendrimers were shown in Figure 3, which revealed the formation of spherical shape with irregular surface. SEM micrographs of drug loaded PEGylated dendrimers of drug showed that the drug loaded dendrimers were more or less spherical in shape (PEGylated 5.0G EDA-PPI dendrimers) and that the dendrimers were agglomerated.

Particle size and polydispersity index

The particle size of synthesized plain PPI dendrimers, PEGylated dendrimers, Prednisolone loaded PEGylated dendrimers were analyzed by Malvern particle size analyzer. The formulations are intended to know the size, the sizes varied with the molar concentration of PEGylated dendrimer and drug substances. It was observed that when the drug ratio is less the size altered slightly but the drug ratio is higher the size is increasing considerably due to the non-covalent bond of drug and PEGylated dendrimer proves the agglomeration, were by the size is large. Even though overall distribution of all the formulations size were seen between 78 ± 0.8 to 110.6 ± 2.2 nm. This will allow the bio addictive nature of the formulation. The Polydispersity index value of the optimized formulation is indicated as 1.000. The particle size of dendrimer was the main factor for diffusion through lipid layers in the system. Particle size of 20-200 nm were easily transported in the cell wall of the cancerous cells by passive diffusion.

Differential scanning calorimetry

Curves of DSC clearly suggested the difference between the physical mixture of plain drug and encapsulated drug - PEGylated PPI 5.0G dendrimer complex. The plain Prednisolone DSC curve showed no endothermic or exothermic peak at its melting point up to 214°C. PEGylated PPI 5.0G dendrimers experienced an endothermic peak near 56.20°C. In physical mixture of Prednisolone with PEGylated PPI 5.0G dendrimers both the peaks of Prednisolone and PEGylated PPI 5.0G dendrimer were found near 56.18°C. DSC curve of Prednisolone loaded PEGylated PPI 5.0G dendrimers the peaks of plain Prednisolone and PEGylated dendrimers almost disappeared and a very broad peak near 94.14°C was observed. The compatibility of drug dendrimer as presented in Figures 3-6.

In vitro drug release

A comparative evaluation of the effect of PEGylation on the release of prednisolone from EDA-PPI dendrimer-(NH2)64 was performed. Among the three formulations PEGylated dendrimers (1:1) gave relatively slower release of prednisolone when compared with (1:0.5 or 1:2) ratio of PEGylated dendrimers. The pure prednisolone released 62.5% in 8 h while drug loaded PEGylated 5.0G EDA-PPI dendrimers released only 16.5% and 99% in 8 and 48 h, respectively. The release patterns of both the optimized formulations were shown in Figure 7.

Release kinetics study

With regard to the diffusion of the optimized formulation of drug loaded PEGylated PPI 5.0G dendrimers of prednisolone was monitored for 8 h to so on up to whole drug released from the system. The release of the prednisolone from the dendrimer system is characterized by a sustained release of the drug over the period of 48 h to 80 h respectively. The release involves two different mechanisms of drug molecules diffusion and polymer degradation.

The formulation of the drugs showed that the linearity of (R^2 = 0.985). The zero order (R^2 = 0.971) and peppas equation (R^2 = 0.988). The release kinetic was often used for comparative purpose and relating the release parameters with important in bioavailability and used to study influence of formulation factors on the drug release for optimization as well as control of drug release from dendrimers. The profile of the drugs release from the PEGylated dendrimer system showed fitting with peppas plot with zero order release kinetics and indicated non fickian diffusion mechanism for the release of the drugs respectively.

S. No	Formulation code	Ratio of (dendrimer: drug) In mol. con	% of drug entrapped
1.	DLDP	1:0.5	7.28 ± 1.9
2.	DLDP	1:1	89.20 ± 0.2
3	DLDP	1:2	48.4 ± 1.2

Table 1: Drug entrapment efficiency of Prednisolone loaded PEGylated dendrimer.

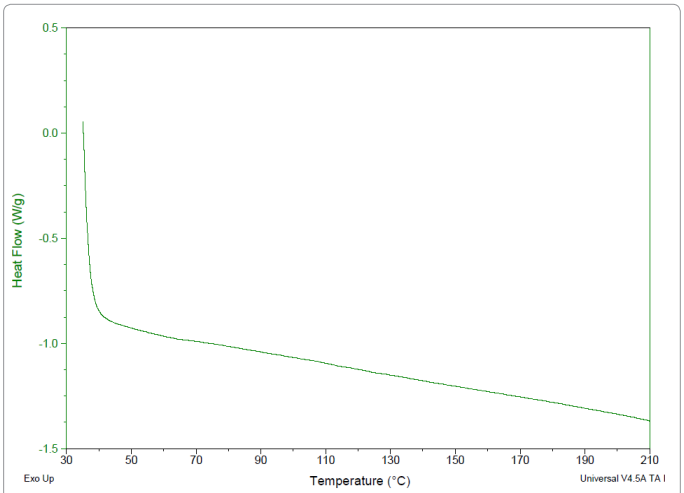

Figure 3: DSC curve of plain prednisolone drug.

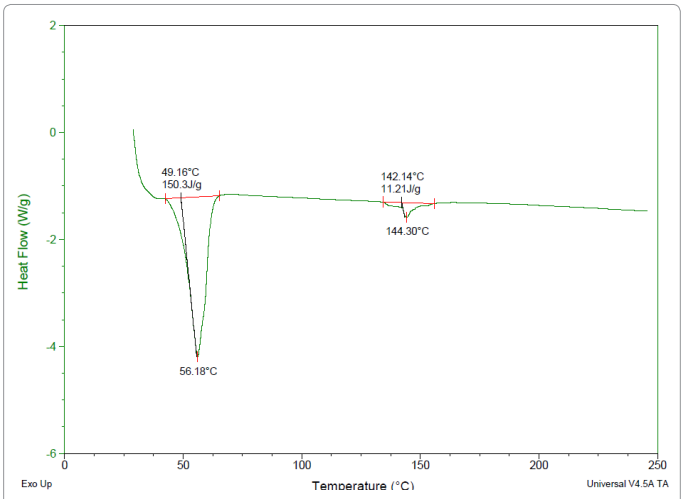

Figure 4: DSC curve of PEGylated dendrimers.

Stability study of drug loaded PEGylated PPI dendrimers

The stability study was performed for optimized formulations of prednisolone at 40±2° C for 4 weeks neither change in its appearance and redispersing ability nor significance difference in potency. The drug content and the release also not changed.

Pharmacokinetic study

The maximum plasma concentration was observed for plain prednisolone as compared to drug loaded PEGylated PPI dendrimers.

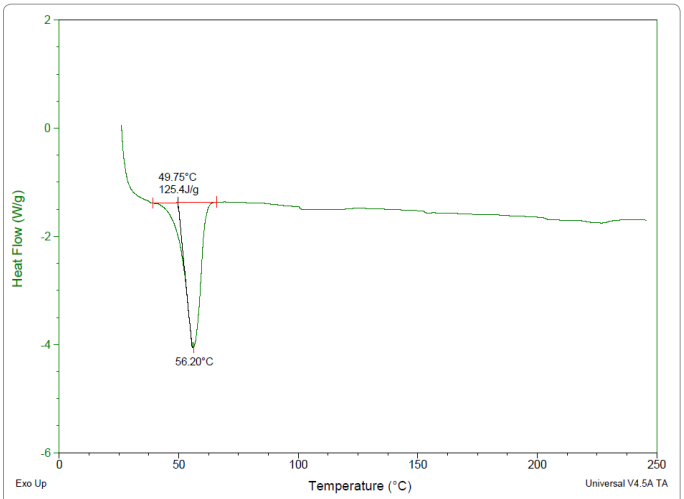

Figure 5: DSC curve of physical mixture of drug.

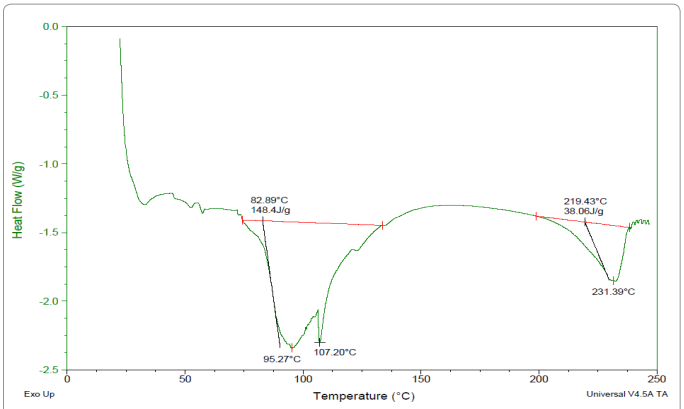

Figure 6: DSC curve of Prednisolone loaded PEGylated dendrimers.

The Cmax values attained after i.v administration were 287.02 ng/ml for plain prednisolone and drug loaded PEGylated PPI dendrimer shows 294.2 ng/ml. The AUC $_{(0\rightarrow\infty)}$ (ng/ml/hr) for plain prednisolone and drug loaded PEGylated PPIdendrimer was found to be 908.19 and 10768.12 ng/ml/hr, respectively. When apparent $t_{1/2}$ of formulation was compared the parameter was 0920539, 0.684725 and 33.72552, 30.21449 hours for plain drug and drug loaded PEGylated PPIdendrimer respectively. After i.v administration $t_{1/2}$ increased in the case of drug and drug loaded PEGylated PPIdendrimer as compared to the plain prednisolone, which is attributed to the polyethylene glycol (PEG) coating of PPI dendrimer that rendered the formulation more "biostable" compared to plain prednisolone. Further PEGylated PPI dendrimer formulation of prednisolone demonstrated highest $t_{1/2}$ probably because of the size of the dendrimer and its ability to impart better" stealth" features as compared to plain drug. The higher AUC values of PEGylated PPIdendrimer formulations also indicated that the formulations were of long circulating nature. Previous reports also have suggested that the long circulating and sustained release property of PEGylated dendritic systems. The values of pharmacokinetic study were calculated and presented in Table 2.

Antileukemic activity

The antileukemic activity was assessed by use of the criterion T/C%. The results obtained from this study on the effect of Prednisolone and its Prednisolone loaded PEGylated Polypropyleneimine (PPI) dendrimer on BDF_1 hybrid mice-bearing AML-193 leukemia are shown in Table 3. According to these results, the free Prednisolone exhibited a pronounced and dose-related antileukemic activity on mice-bearing AML-193 leukemia. An increase of the free Prednisolone dose over 0.25 mg/kg × 3, i. p., caused an increase in its acute toxicity. This fact was registered by the progressive decrease in the ratio T/C (treated/control). The dose of the free Prednisolone of 1.5 mg/kg × 3, i. p., was toxic (T/C% < 125%). The Prednisolone loaded PEGylated Polypropyleneimine (PPI) dendrimer exhibited an antileukemic activity against acute lymphocytic AML-193 in BDF_1 mice, in four of the used doses – from 0.5 mg/kg × 3 to 8.0 mg/kg × 3, i. p., with T/C% varying between 195.1% and 270.1%. The experimental results

Formulation code	AUC	AUMC	$T_{1/2}$	T_{max}	C_{max}	MRT
Plain prednisolone	846.975	2137.95	0.920539	3	292.6	2.87
Prednisolone loaded PEGylated dendrimers	9441.895	209673.1	33.72552	10	290.3	51.88

Table 2: Pharmacokinetics parameters of plain prednisolone and prednisolone loaded PEGylated PPI dendrimers in albino rats plasma.

Drug and formulation	Dose (mg/kg) x 3, i.p	MST (in days)	T/C (%)
Prednisolone	0.25	19.4	179.6
	0.5	17.3	166.3
	1.0	14.8	142.3
	1.5	12.5	120.1
Prednisolone loaded PEGylated PPI dendrimer	0.5	20.3	195.1
	1.0	21.6	207.6
	2.0	23.2	223.0
	4.0	26.7	256.7
	8.0	28.1	270.1
Untreated control	0	10.8	-

MST: Mean Survival Time (days); T: Survival Time of Treated Mice (days); C: Survival Time of Control Mice (days); Significant antileukemic effect at T/C% > 125% was accepted.
Toxic dose at T/C% < 125%.

Table 3: Antileukemic activity of free Prednisolone and Prednisolone loaded PEGylated PPI dendrimer on BDF1 hybrid mice-bearing K-562 leukemia.

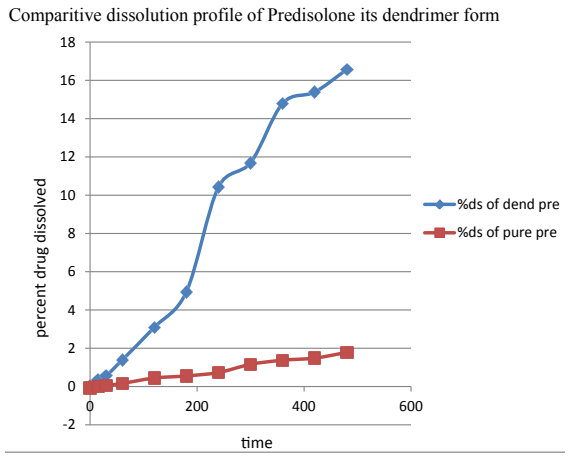

Figure 7: Comparative dissolution profile for pure Prednisolone and prednisolone dendrimers.

on activity of the Prednisolone loaded PEGylated Polypropyleneimine (PPI) dendrimer showed that an increase in dose levels of equivalent to the free drug led to an increase in the ratio T/C, indicating lower toxicity. The dose of 8.0 mg/kg × 3, i. p., was not toxic (T/C% = 270.1%).

The antileukemic activity of the Prednisolone loaded PEGylated dendrimers are shown more significant activity than the activity of free Prednisolone that was favorable by clinical point of view. The chemical and pharmacological investigations in this field are in progress, aiming to analyse the results and trying to design better formulation of selected antitumor drugs with dendrimers, for potential clinical use.

Conclusion

5.0G EDA-PPI dendrimer were PEGylated using DCC with poly(ethylene glycol). For prolonged release of prednisolone, ethylene diamine initiator core EDA-PPI dendrimers has been found to be suitable for modification by PEGylation. By transporting the drug at a controlled rate for a prolonged period of time, thus optimizing the efficacy by minimizing fluctuations in plasma drug concentration this study expect that the approach will improve the management of drug therapy in leukemia patients.

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Conflict of Interest

The authors worked in this research not showing any conflict of interest to publish this article.

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