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RESEARCH ARTICLE

Performance Evaluation of PPI Dendrimer Based Valsartan and Fenofibrate Formulations.

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ABSTRACT

The purpose of this investigation was to evaluate the performance of poly (propylene imine) (PPI) dendrimers, with three different drug concentrations, to be used as drug carriers. Drug–dendrimers complexes were investigated for dissolution studies, in vitro drug release studies, and for stability studies. The formation of the complexes between drug molecules and dendrimers were characterized by the FTIR, DSC and SEM spectra of these complexes, showing the appearance of the bond formed between the functional groups of the drug (COOH) and dendrimers (NH2). The drug–dendrimer complexes displayed the controlled release action during in vitro release studies. Pure valsartan (VAL) and fenofibrate (FB) was released in 5 h whereas the PPI dendrimers–VAL-FB complexes released the drug up to 24 h. Formulations with PPI dendrimers were subjected to accelerated stability studies and were found to be most stable in dark, low temperature (0°C) whereas the dark, RT was most suitable storage conditions for formulation with PPI dendrimers.

KEYWORDS: Dissolution, PPI dendrimer, Valsartan, Fenofibrate

INTRODUCTION:

Currently available all novel drug delivery systems basically involve the use of lipids or polymers. Each type of system has its limitations: lipid based drug delivery systems (i.e., liposomes, solid lipid nanoparticles, nanostructured nanocarriers) have poor physical stability, drug leakage, difficulty in drug targeting [1, 2] and low drug loading capacity due to the formation of a perfect lipid crystal matrix [3] whereas polymer based systems use linear polymers which are polydisperse in nature, in addition to regulatory issues and scaling up problems. Dendrimers are a unique class of synthetic macromolecules having a highly branched, three dimensional, nanoscale architecture with very low polydispersity (1.00002–1.005) and high functionality. The unique structure makes dendrimers an excellent building block to create an ideal polymeric drug-delivery system with multiple functionalities, which is otherwise difficult to achieve with linear polymers. The basic advantage of dendrimers is to deliver drugs efficiently and effectively, at the same time they also improve the biopharmaceutical and pharmacokinetic properties of drugs [4]. Various studies have been carried out to use dendrimers as drug delivery via various routes of administration: oral [5-7], intravenous [8-13], transdermal [14, 15], and ocular [16, 17]. Among the three basic family of dendrimers: poly (amidoamine) (PAMAM), diaminobutane (DAB) and polypropyleneimine (PPI), PAMAM dendrimers have been extensively used in drug delivery because they allow the precise control of size, shape and placement of functional group (dimensional stability), controlled method of synthesis, minimum toxicity and wide availability. So the basic objective of this project was to evaluate the performance of three different drug concentrations with G5 PPI dendrimers to be used as drug carriers and to simultaneously develop the controlled release formulation of lipid lowering drug FB and an anti-hypertensive drug VAL. The reason behind to develop this formulation is that the patient suffered with hypercholesterolemia requires a long term treatment and secondly to incorporate the anti-hypertensive drug also.

2. MATERIALS AND METHODS:

2.1. MATERIALS:

G5-PPI dendrimers were synthesized. Valsartan (VAL) and Fenofibrate (FFB) were supplied by Eurokem Laboratory, Chennai. Cellulose dialysis tubing (Mw ∼1000) and membrane filter of pore size 0.2_m were purchased from Himedia Lab. (Mumbai, India). Rest all chemicals were of analytical grade and were purchased from CDH (India).

2.2. Characterization of drug–dendrimer complexes FTIR spectrums of VAL-FB and PPI dendrimers–VAL-FB complexes were obtained by means of a FTIR spectrophotometer. The samples were prepared by the potassium bromide disk method and measurements were attempted with the accumulation of 20 scans and a resolution of 4 cm−1 over the range o f 400–4000cm−1. After running the spectra, significant peaks relating to major functional groups were identified; spectra of the subsequent sample of the same compound were compared

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with the original. Further DSC studies were also carried out to confirm the complexation of drug and dendrimers.

2.3. DISSOLUTION STUDIES:

The dissolution of pure VAL-FB and PPI dendrimers–VAL-FB formulations was determined in simulated gastric fluid (SGF) and USP dissolution medium pH 7.0 phosphate buffers. Three ml of drug–dendrimer formulations were taken in round bottom flask and lyophilized. These lyophilized formulations and pure VAL-FB were exposed to the 900 ml of dissolution medium, at 37±0.5°C and 50rpm on magnetic stirrer. At scheduled intervals, 2ml of samples were withdrawn and replenished the dissolution medium with the same volume. After appropriate dilutions, the amount of drug dissolved as a function of time was determined by RP-HPLC at 247 nm.

2.4. IN VITRO DRUG RELEASE STUDIES:

In vitro drug release from the different drug–dendrimer complexes was determined using the dialysis tube diffusion technique. Three ml solution of drug–dendrimer complexes were placed in the hermetically tied dialysis sacs, separately. These dialysis sacs were placed into 80 ml of 0.1Mphosphate buffer saline (PBS) pH 7.4, kept at 37±0.5°C with continuous magnetic stirring to maintain sink conditions. At scheduled intervals, 1ml of sample was withdrawn from the external medium and replaced with the same volume of fresh PBS to maintain the sink conditions. After appropriate dilutions, the amount of drug released as a function of time was determined by RP-HPLC at 247 nm.

2.5. STABILITY STUDIES:

The dendrimer–drug formulations were kept in amber colored and colorless vials at 0°C, room temperature and 60°C for a period of 5 weeks. The samples were analysed initially and periodically for up to 5 weeks for any precipitation, turbidity, crystallization, change in color, change in consistency and increase in drug loss. The drug leakage was indirectly determined by checking the increase in release rate of drug from the formulations after storage. The obtained data were used for the analysis of any physical or chemical degradation at specified storage conditions.

3. RESULTS AND DISCUSSION:

3.1. CHARACTERIZATION OF DRUG–DENDRIMER COMPLEXES

The use of the dendrimers as drug delivery vehicle depends on their ability to form a complex with the drug and the formation of drug–dendrimer complex further depends on the nature of the core–surface groups of the dendrimer, electrostatic interaction between the dendrimer and the drug and the ability of the drug to form a conjugate with the dendrimers through chemical bonding. So the drug–dendrimer complex formation between the VAL and dendrimers and FB was loaded into the PPI-VAL conjugated dendrimer used in this project were characterized by their FTIR, DSC and SEM.

All the spectra are given in Fig 1. [A] FTIR spectra of pure VAL [B] FTIR spectra of pure FB [C]FTIR spectra of pure 5.0G PPI dendrimer[D] FTIR spectra of PPI-VAL-FB complex. Fig 2. [A] DSC spectra of pure 5.0G PPI dendrimer[B] DSC spectra of PPI-VAL-FB complex. Fig 3. SEM of PPI-VAL-FB complex.

3.2. DISSOLUTION STUDIES:

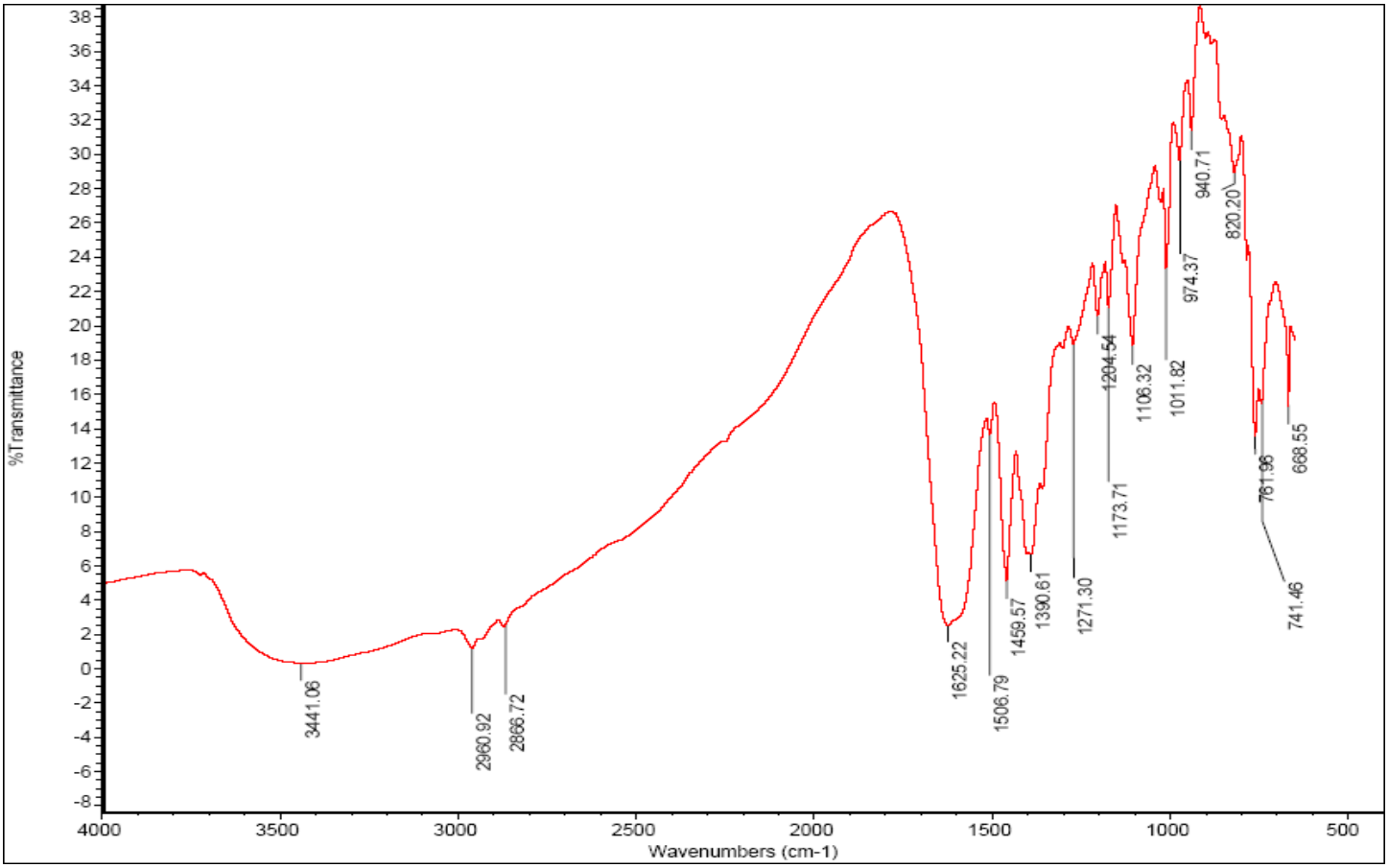
The dissolution of pure drug and drug–dendrimer complexes was determined in USP dissolution medium pH 7.0 phosphate buffer with three different drug dendrimer ratio. The results are shown in Figs. 4, 5 and Table. 1 & 2. At the end of 12 h, the dissolution of the VAL and FB from the drug–dendrimer complexes was significantly good for drug:dendrimer (1:1) than other two ratios. This may be the result of interaction between drug and dendrimer molecules which leads to the enhancement of solubility of the drug in dissolution medium.

3.3. IN VITRO DRUG RELEASE STUDIES:

In vitro release of uncomplexed VAL and FB and drug–dendrimer formulations was performed in phosphate buffer saline pH 7.4. Pure VAL and FB was released 89%, 91% respectively in 5 h whereas drug–dendrimer formulations displayed initial rapid release followed by the delayed release of the drug in later half. This is possibly due to initial release of the drug encapsulated in dendrimer cavities and drug attached to surface groups (primary amines). The internal secondary nitrogens are basic and are therefore involved in deprotonating the acidic drug molecules. These quaternized nitrogens bind the counter ions such as carboxylate and hydroxyl ions and control their dissociation.

3.4. STABILITY STUDIES:

The stability of G5-PPI dendrimers were evaluated at various conditions of temperature (0°C, RT and 60°C) after keeping in dark (in amber colored vials) and under light in colorless vials. The observed results suggested that the dendrimer-based systems are stable even at elevated temperature up to 60°C if kept in dark. Formulations with amine surface groups were found to be most stable in dark, low temperature (0°C) whereas the dark, RT was most suitable storage conditions for formulation with PPI dendrimers.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1506.79
1459.57
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1271.30
1204.54
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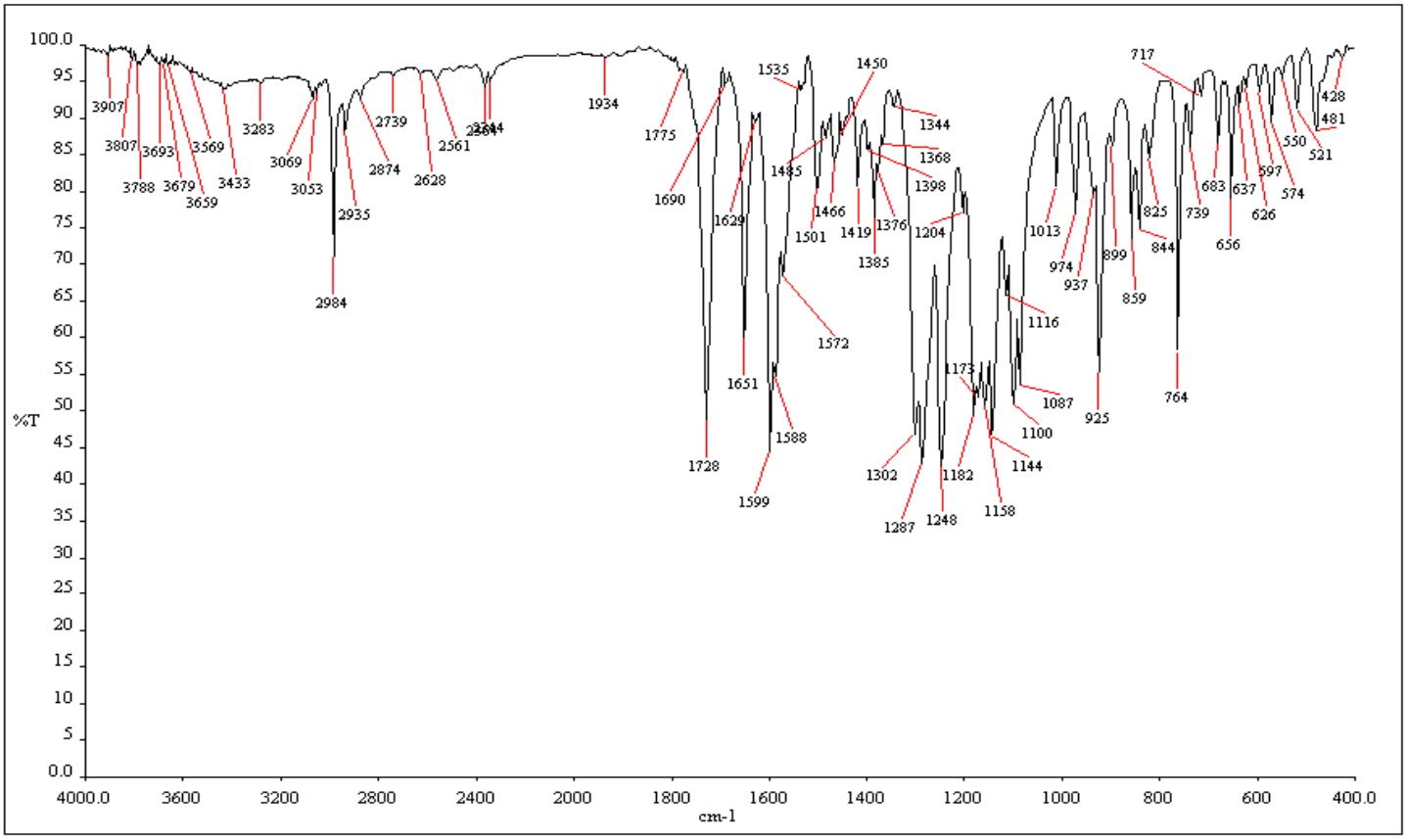
668.55

(A)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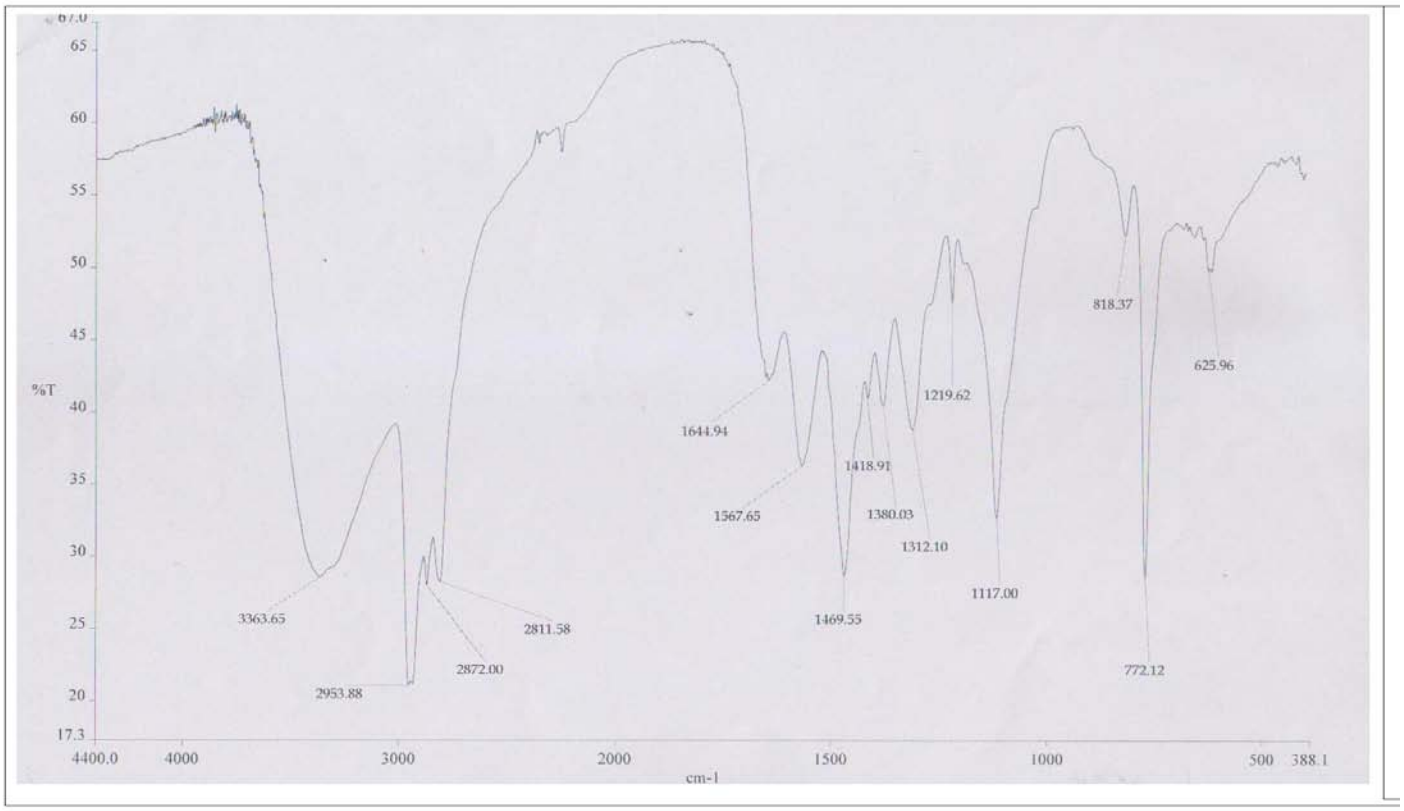
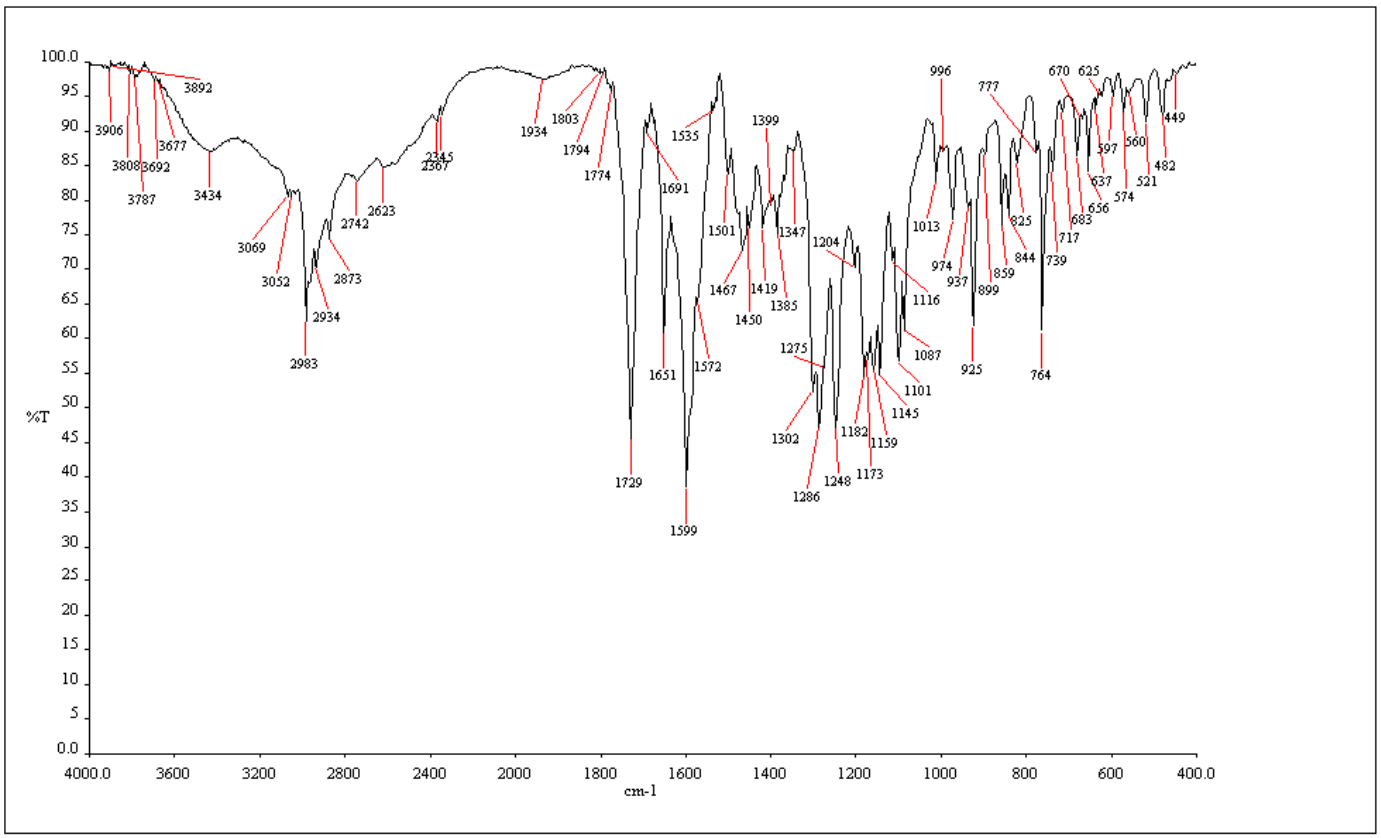
(B)

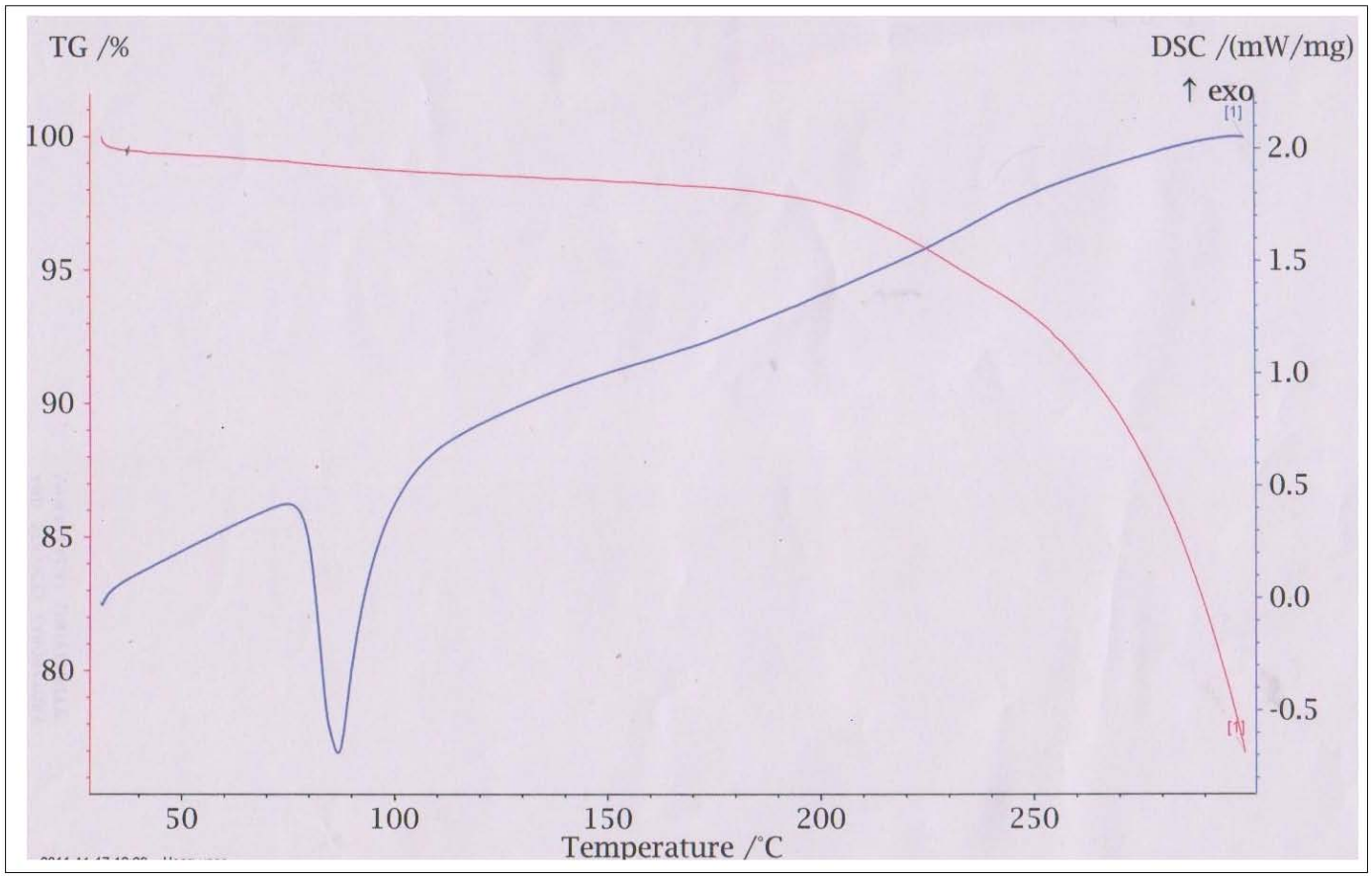


(C)

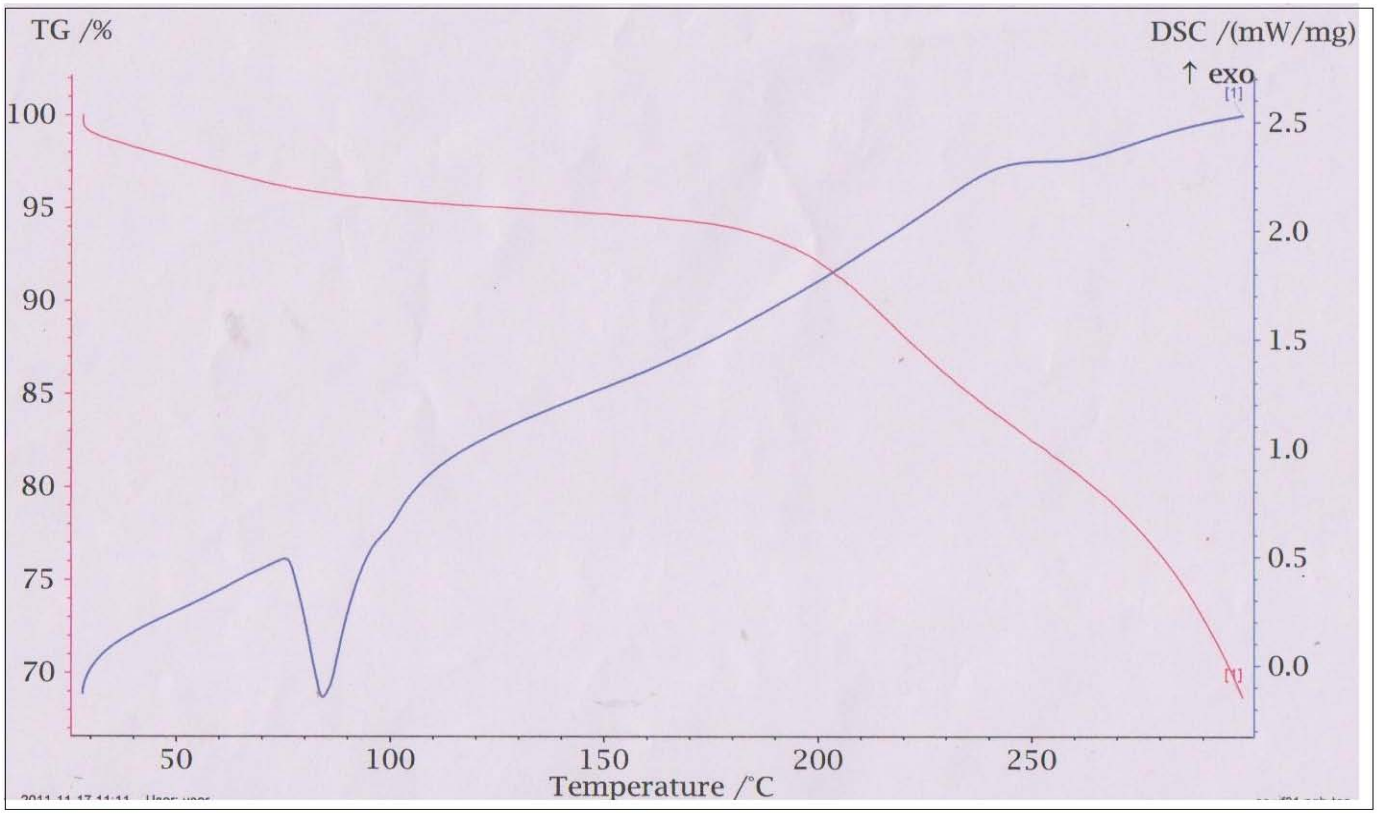


(D)

Figure No.1: [A] FTIR spectra of pure VAL [B] FTIR spectra of pure FB [C] FTIR spectra of pure 5.0G PPI dendrimer[D] FTIR spectra of PPI-VAL-FB complex



(A)



(B)

Figure No. 2: [A] DSC spectra of pure 5.0G PPI dendrimer[B] DSC spectra of PPI-VAL-FB complex

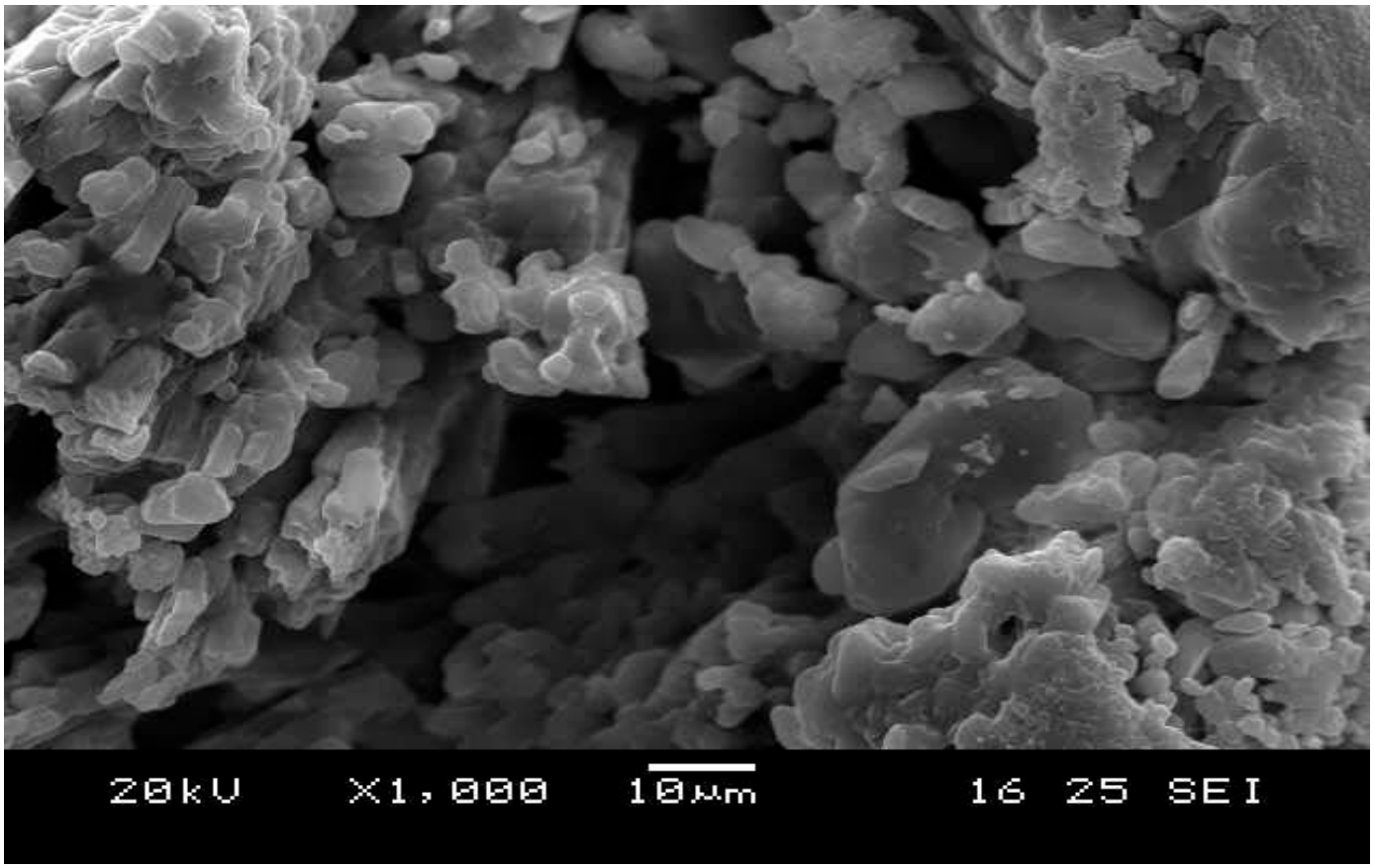


Figure No. 3: SEM of PPI-VAL-FB complex

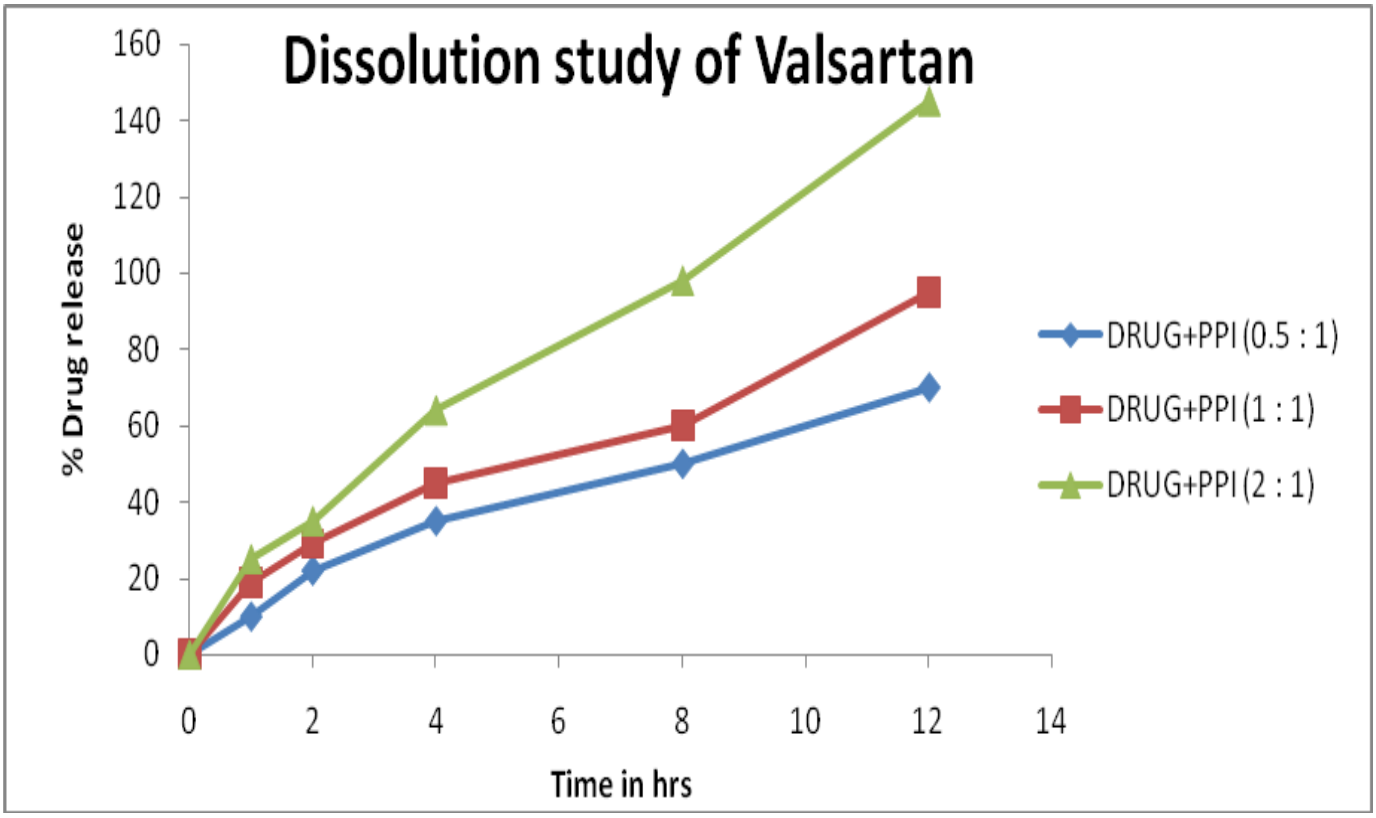


Figure No. 4: Dissolution study of VAL

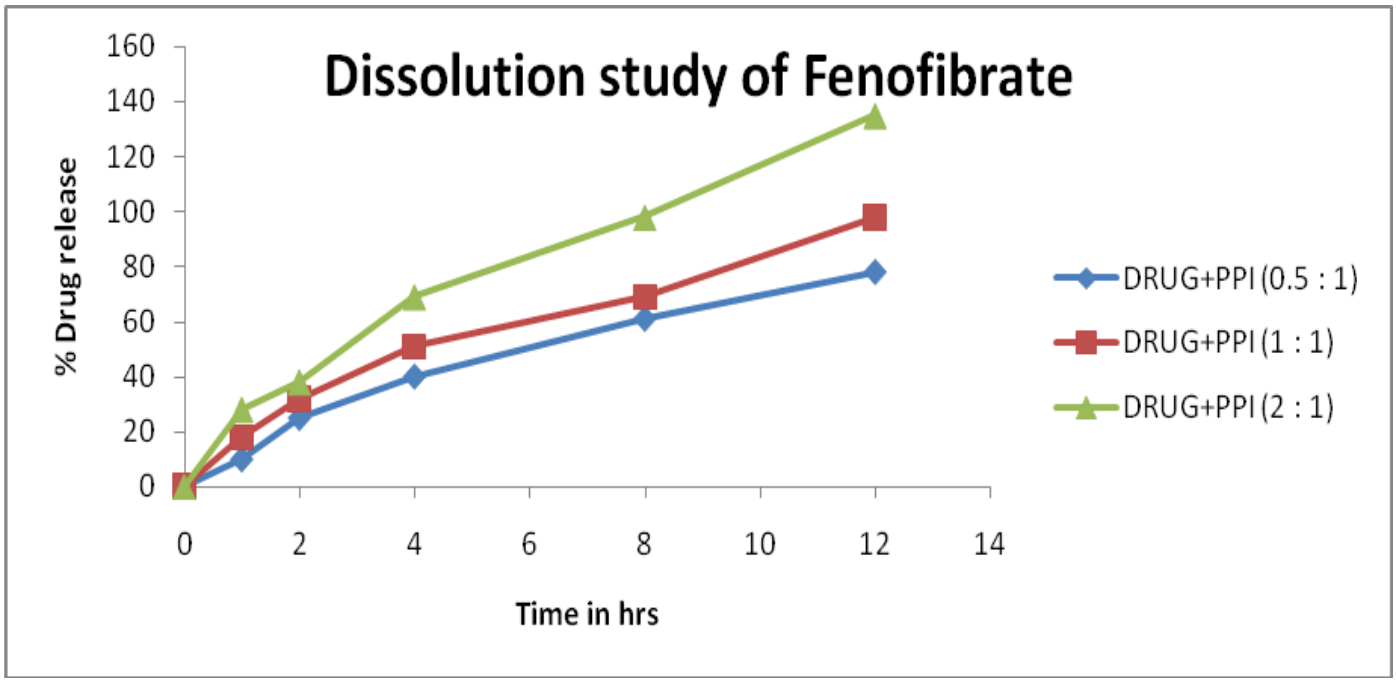


Figure No. 5: Dissolution study of FB

Time in hrs	% Drug release for VAL		
	DRUG+PPI (0.5 : 1)	DRUG+PPI (1 : 1)	DRUG+PPI (2 : 1)
0	0	0	0
1	10	19	25
2	22	29	35
4	35	45	64
8	50	60	98
12	70	95	145

Table No. 1: % Drug release for VAL

Time in hrs	% Drug release for FB		
	DRUG+PPI (0.5 : 1)	DRUG+PPI (1 : 1)	DRUG+PPI (2 : 1)
0	0	0	0
1	10	18	28
2	25	32	38
4	40	51	69
8	61	69	98
12	78	98	135

Table 2: % Drug release for FB

4. CONCLUSION:

PPI dendrimers could be exploited to develop the formulation of a weakly acidic and practically water insoluble drug VAL and FB. The dendrimers improve the dissolution of VAL and FB, however, the enhancement depends on the concentration of dendrimer and the surface functional group of the dendrimer. In addition, they also offer the advantage of controlled release of the drug from the drug–dendrimer complexes. Among the various generation G5-PPI dendrimers show better in vitro performance. G5-PPI dendrimer results in to the better dissolution, slower release of the drug, more biocompatibility and more stability of the drug compared to the other generation PPI dendrimer. However, the in vivo potential of the formulations is under investigation.

5. ACKNOWLEDGEMENTS:

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