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Research Article

TRIMESOYL MELONATE ESTER BASED 1ST TIER DENDRIMERS WITH INCREASING DIALKYL CHAIN AS A POTENTIAL DRUG CARRIER FOR SILIBININ ANTICANCER DRUG

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ABSTRACT

Silibinin (SB) is a flavonoid with an eminent anticancer activity but poorwater solubility, whichrestricts its biomedical applications. Considering this as a potential challenge, the SB binding and release were studied usingtrimesoyl 1, 3, 5-tridipropyl malonate (TTDPM), trimesoyl 1, 3, 5-tridibutyl malonate (TTDBM) and trimesoyl 1, 3, 5-tridihexyl malonate (TTDHM)1sttier dendrimers. The SB binding with TTDPM, TTDBM and TTDHM having dipropyl (-CH2CH2CH2)2, dibutyl (-CH2CH2CH2-CH2-)2 and dihexyl (-CH2CH2CH2CH2CH2CH2)2dialkyl chainsare attained from FTIR, DSC, DLS and SEM studies. UV-Vis spectroscopy has depicted in vitro4 %/h release of SBin PBS + 10 % DMSO (PD) medium at 37 0C. The SB release from TTDPM, TTDBM and TTDHM with dipropyl, dibutyl and dihexyl dialkyl chains are in1.61: 1.43: 1.12% ratio.The results of this study can provide new insights in the development of 1st tier dendrimers as drug delivery systems for SB with a controlled and sustained release tendency.

INTRODUCTION

Currently, the development of cost-effective and far less time-consuming drug design and delivery systems are required for the active development in the fields of biomedical and pharmaceutical sciences. There is a significant thrust prevalent in terms of the exactness and effectiveness of the corresponding drug systems that sometimes lead to a little higher dosage of delivered drugs resulting in damage to the normal cells and causing of variable side effects: headache, skin problems and others (Zhuo *et al,* 1999).The development of formulations of highly efficient drug binding materials have been a century old challenging task for better and safer curing of the disease because an effective curing depends on an efficacy of the corresponding drug delivery system. Through the control of adrug release system, side effects of the drugs can be minimized which could significantly lead to an improvement in the drug functioning efficacy. The binding of a drug is regulated in a most wanted manner which leads the drug transportation to the targeted sites. Most importantly, it shows sustained release that facilitate the biochemical functioning by avoiding structural exchange during the whole process (Nalylor *et al*, 1989, Jansen *et al*,1994, Hawker *et al*, 1993, Malik *et al*, 1999)**.**The SB is a flavanone with animmunomodulatory effectsuch as anticancer, chemopreventive and antioxidant activities (Fig. 1) (Morazzoni *et al*, 1995). Due to poora water solubility, the SB is normally administered through oral route in an encapsulated form (Luper 1998, Morazzoni *et al,* 1993, Pepping 1999). It is also due to this fact the SB requires novel formulations for its betterment to enhance its bioavailability and subsequently improve its bioactivity. One such formulation of SB is composed of a complex silipide, which further consists of SB and phosphatidylcholineal most ten times more effective than pure SB (Kidd an Head, 2005).Arcari *et al* have proposed an inclusion complex of SB with β-cyclodextrinupto≈ 18 times more soluble than SB alone(Arcari*et al*, 1992).The problem of bioavailability of SB has been highlighted by several studies, with majority of them highlighting poor absorption (Comogli *et al*, 1995, Giacomelli *et al*, 2002) and degradation through the intestinal fluid or its poor solubility (Madaus *et al*, 1976; Gabetta *et al*, 1988). These finding confirm that a comparatively higher dosage of SB is required to reach effective therapeutic plasma levels. But no systematic studies are report yet. Interestingly, some studies have also shown that higher intake of SB dose results in a side effect responsible for

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bile secretion and bile flow associated with it(Tyler 1994).Thereby, bioavailability enhancement of SB has been given a fair deal through several studies conducted for improvement to larger extents. Attempts that have been made include encapsulation of SB in a form of complexation with cyclodextrin which produce a double enhancement in SB bioavailability (Valcavi 1993).Similarly, SB has been delivered in the form of poly hydroxyphenyl chroman ones**,** several others soluble derivatives and widely speculated complexation with phospholipids (Skottovaa *et al*, 2000;Vailati *et al*, 1993).Also, for highly efficient drug delivery systems the dendrimers, hyperbranched polymer and nanoparticles as potential materials for drug vehicles(Beezer*et al*, 2003; Miaoa*et al*, 2010; Nie *et al*, 2011).Dendrimers are highly branched having multiple functional groups at terminal position and globular shape with embedded interstices inside in their structures. The exceptional structural features of dendrimers play animmenserole by entering the embedded structures of drug molecules through their tentacles which enables alterations in their structural activities suited for better transportation (Pandya *et al*, 2016). Despite of dendrimer's extraordinary structural attributes to facilitate binding of SB, no scientist has undertaken such investigation in order to make the best use of dendrimers particularly in the domain of drug design. In earlier work, synthesis andcharacterization of dipropyl, dibutyl and dihexyl malonates esters terminated TTDPM, TTDBM and TTDHM have been reported(Undre *et al*, 2013). The TTDPM, TTDBM and TTDHM having a trimesoyl chloride (TMC) as a core and variable dialkyl malonate esters as a branching unit with well-defined size and globular shape, facilitate encapsulation of foreign molecule like anticancer drugs in their interstices as shown in Fig. 2. Thereby, a series of dialkyl (dipropyl to dihexyl) malonate esters terminated dendrimers were chosen for SB encapsulation for better transportation with enhanced stability and minimizing the undesired higherdosages of SB. The increase in the dialkyl chain plays a major role in optimizing thecontrolled release profile of SB with a sustained release as described in this paper.

MATERIAL AND METHODS

Materials

Silibinin, acetone, tween 60and phosphate buffer saline(Sigma Aldrich), DMSO (Rankem India) and corning sterile syringe filter 0.20 µm (Germany)were used as received.

Drug-Dendrimers Complex Preparation

SB-TTDPM, SB-TTDBM and SB-TTDHM complexes were prepared by mixing in (1:1, mol/mol) in 20 mL acetone at constant stirring with 400 rpm for 12 h at RT. After 12 h, the acetone was evaporated at 56^0C in vacuum using Rotavapor (R-210, Buchi, Switzerland). Complex formation was analysed with TLC.

Characterization Methods

FTIR spectra for dendrimers, SB and SB-dendrimershave been recorded with Perkin-Elmer 65 series FTIR spectrophotometer using 1.5 to 2.0 mg sample in a pelletized form with KBr. DSC study was made with DSC 6000 Perkin Elmer from 50 to 250^0C at 10^0C/min heating rate, and 2 mg sample was packed in aluminium pans. A mean diameter (MD) and polydispersity index (PDI) were determined with Dynamic Light Scattering (DLS), Microtrac Zetatrac Metrohome. The 0.2 mg SB, dendrimers and their complexes were separately dissolved in 10 mL Tween 60 (dispersant medium) for DLS analysis. The surface morphology of dendrimers and complexes were studied with SEM, Carl Zeiss, EVO-18, operated at 20 kV. The solid sample was coated with thin layer of palladium and gold in 80:20 ratio by sputtering at 5 µA current up to 60 sec.

In vitro Drug Release Analysis

The 25, 50, 75, 100 and 125 µM SB were dissolved in 100 mLPD for calibration curve. The 10 mg complexes were separately dissolved in 100 mL PD (pH 7.4) and stirred continuously at 500 rpm at 37 ^{0}C in 100 mL beaker.The 3 mL adequate sample was withdrawn through a sampling syringe attached to a sterile syringe filter, 0.20 µm (Corning, Germany) at predetermined time intervals (0-10 h).The collected samples were then analysed for SB content by measuring absorbance at 245, 285 and 330 nm with Spectro 2060 plus model UV/Vis spectrophotometer over 200-600 nm using 1 cm path length cuvette. The SB concentration and release % were determined with Equation (1) and (2)(Hu *et al*, 2003;Kalkotwar*et al*, 2010; Park *et al*, 2005; Ling *et al*, 2008).

$$A = \varepsilon \times l \times c \quad (1)$$

The A absorbance, ε molar absorptivity and l is cell path length (cm). The c is SB composition with 125 µM/L (6 mg SB in 100 mL PD) and A is 2.187 and l is 1 cm, putting these values in Equation 1, the ε = 0.3645 m^2/mmol is found at λ_{max} 330 nm.

$$Drug \quad release \quad (\%) = \frac{SB \quad released}{Amount \quad of \quad SB \quad in \quad substrate} \times 100 \quad (2)$$

In vitro release experiments were performed in triplicate (n=3) for each of SB-dendrimers complexes in an identical manner.

RESULTS AND DISCUSSION

Ftir

FTIR depictsthe presence of characteristics structural functional groups corresponding to specific and unique stretching frequencies. Vibrational bandsappeared at 2977-2887 (dipropyl),2972.3-2882.4 (dibutly) and 3421.8-2874.2 cm^{-1}(dihexyl) malonate esters of TTDPM, TTDBM and TTDHM respectively exhibited the aliphatic -CH_2 symmetric and asymmetric stretching(Figs. 3a-3c). The bandsobserved at 1398.6, 1395, 1391cm^{-1}(-CH_3 bending) and 1463.7, 1468.6 and 1444 cm^{-1}(-CH methylene group)of dialkyl malonate in TTDPM, TTDBM and TTDHM respectively (Figs. 3a-3c). The stretching bandsat 1593.9, 1587, 1472.6 cm^{-1} correspond to π conjugated -C=C and 1622.4, 1623.8, 1603.4 cm^{-1}(-C=O) conjugated with aromatic ringof the TMCcorein TTDPM, TTDBM and TTDHM respectively. The 1732.2, 1734.2 and 1730 cm^{-1} bandsdepicted ester -C=0 stretching in TTDPM, TTDBM and TTDHM respectively and 1642.9 cm^{-1} depicted -C=O stretching of SB (Figs. 3a-3d). Thus,it is expected that peaks appearing from 1732.2 to 1642.9 cm^{-1}region reflects in spectra of SB-dendrimers complexes. These peaks correspond to -C=O groups,with a slightshift at lower region due to hydrogen bond (HB)mediated interactions of -C=O of dendrimers and -OH in SB (Fig. 3a-3g).The FTIR spectra of SB showed a broad -OH band at 3457.8 cm^{-1} and -C=O band

about 1642.9 cm^{-1} andshifted to a slightly higher region at 3562.7 and 3462.7 $cm^{-1}$with SB + TTDPM and SB + TTDBMrespectively (Figs. 3d-3g). However,with SB + TTDHM, the band obtainedis slightly shifted to lower band at 3454.5 cm^{-1}. This is due to the presence of an additional -CH_2 group with SP^3 hybridization pattern that also influenced on HB bond interaction of -OH and -C=O.Also, the -C=O conjugated with aromatic ring of TMCappears as slightly shifted in higher region at 1640.2 cm^{-1} in the complexes suggested that formation of HB interaction facilitates the encapsulation of SB. The shifting occurs due tochanges in electron densitywith respect to oxygen and considerably disturbed due to the formation of the HB.

The asymmetric stretching of (-C-O-C-) in dialkyl malonate esters of TTDPM, TTDBM and TTDHM were observed at 1321, 1243.8 and 1243.8 cm^{-1} respectively. These bands are also obtained in SB-dendrimer complexes with slightly variation due to the structural changes incorporated by dendrimers in respective complexes (Figs. 3a-3g).The changes in spectral features of dendrimers during encapsulation of SB were obtained due to significant HB and hydrophobic interactions are found. However, higher spectral changes in SB-TTDHM have inferred a higher SB binding potential of TTDHM due to additional -CH_2 in dihexyl malonate as compared to TTDPM and TTDBM indicated a specific and significant contribution of -CH_2 with additional sp^3 hybridization for HB and hydrophobic interactions. Thereby, a series of variable dialkyl chain of dendrimer structures could be attributed to their involvement in interaction with SB for encapsulation. Thesevariable dialkyl malonate chainsalso initiate tentropic and enthalpic driven activities because of oscillations of their highly branched tentacles when they enter within the networks of HB.In case of such tentacles the intermolecular multiple force theory (IMMFT) play animportant role for higher binding with SB in the interstices of dendrimers. From these results, it is evidently depicted that molecular mechanism of HB and hydrophobic interactions between dendrimers and SB differ with a chemical structure along with a significant role of surface functionality of TTDPM, TTDBM and TTDHM dendrimers.

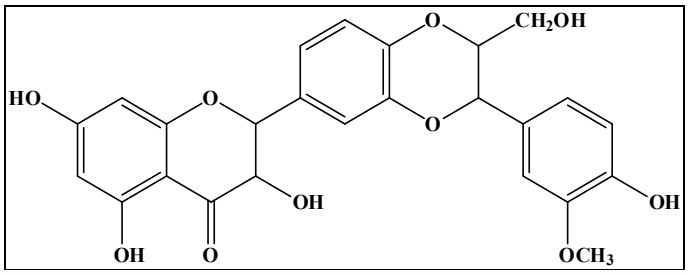

Fig 1 Chemical structure of silibinin

Fig 2 The drug binding mechanism of TTDHM dendrimers

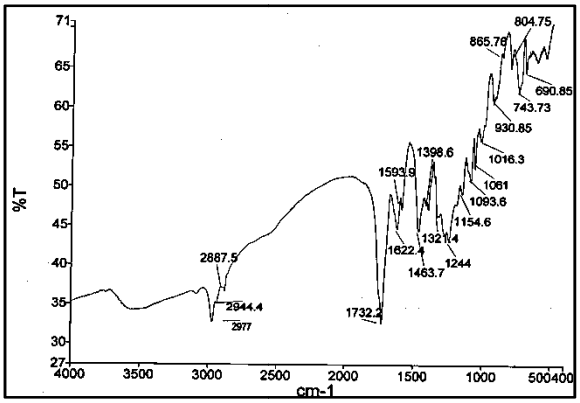

Fig 3a FTIR scan of TTDPM

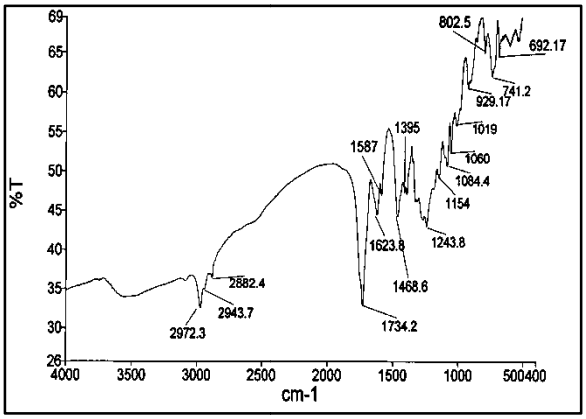

Fig 3b FTIR scan of TTDBM

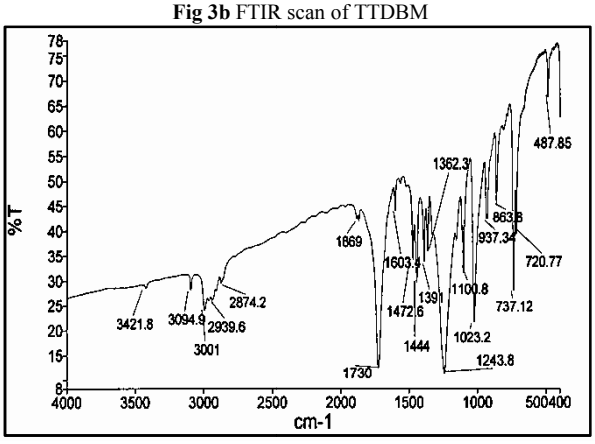

Fig 3c.FTIR scan of TTDHM

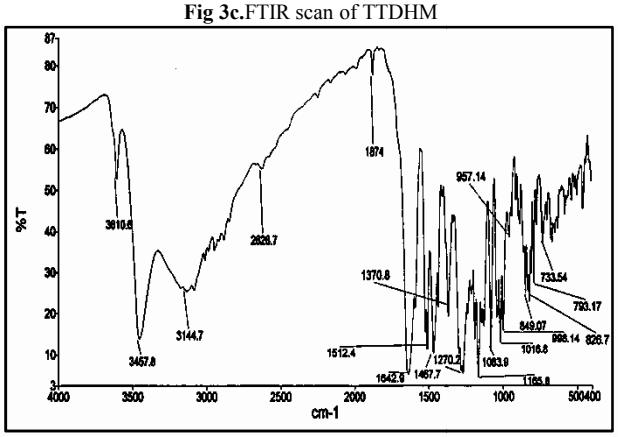

Fig 3d.FTIR scan of SB

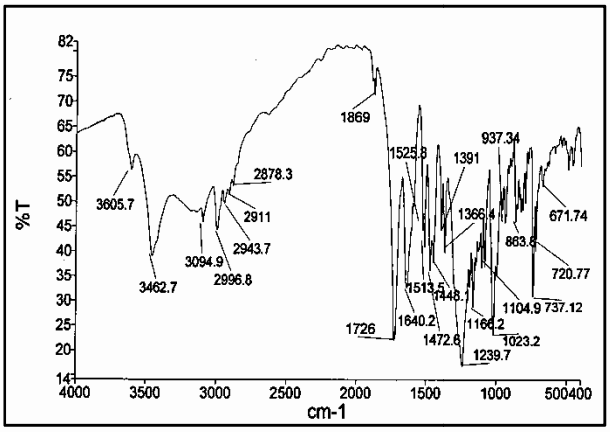

Fig 3e.FTIR scan of SB-TTDPM

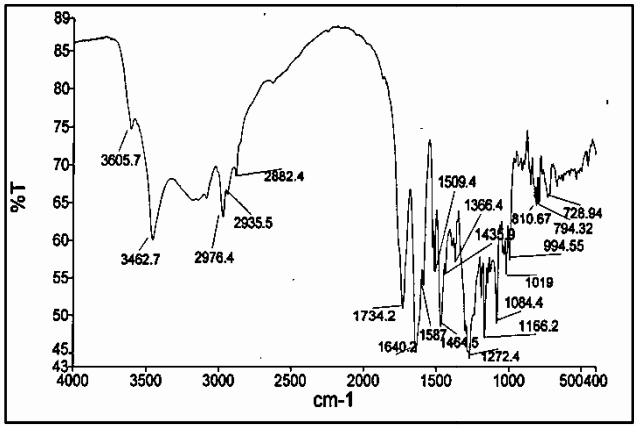

Fig 3f.FTIR scan of SB-TTDBM

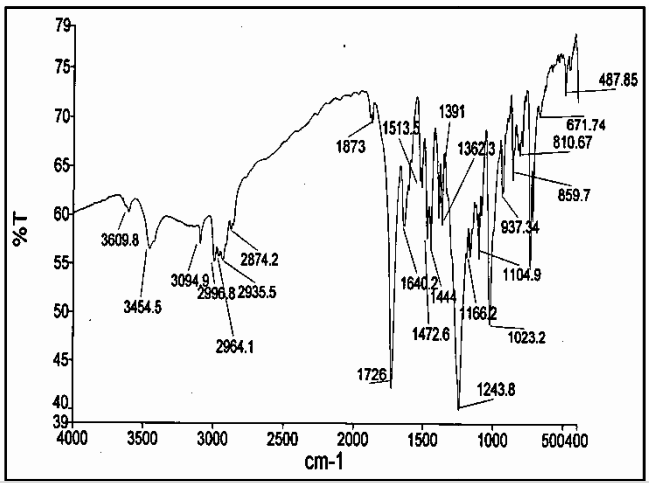

Fig 3g.FTIR scan of SB-TTDHM

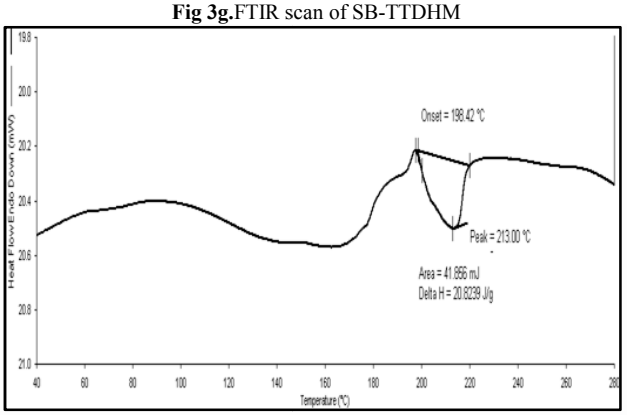

Fig 4a DSC thermogram of TTDPM

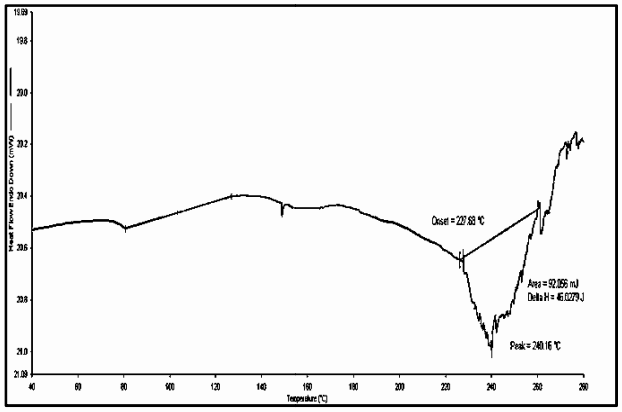

Fig 4b DSC thermogram of TTDBM

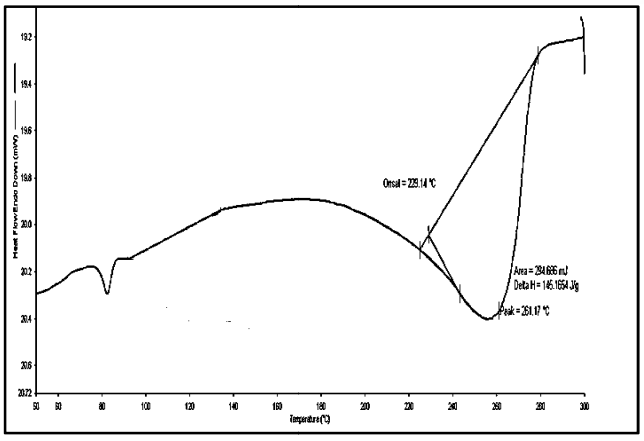

Fig 4c DSC thermogram of TTDHM

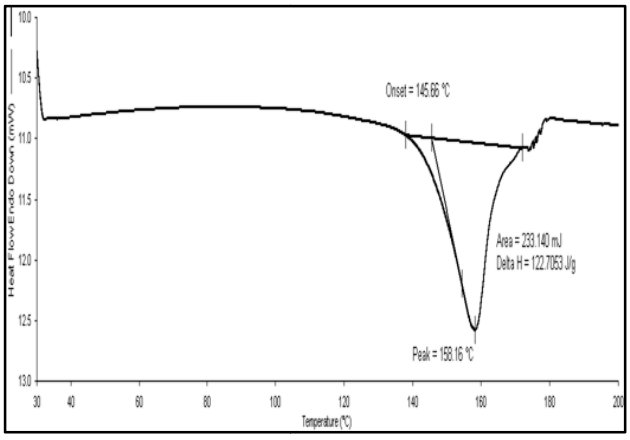

Fig 4d DSC thermogram of SB

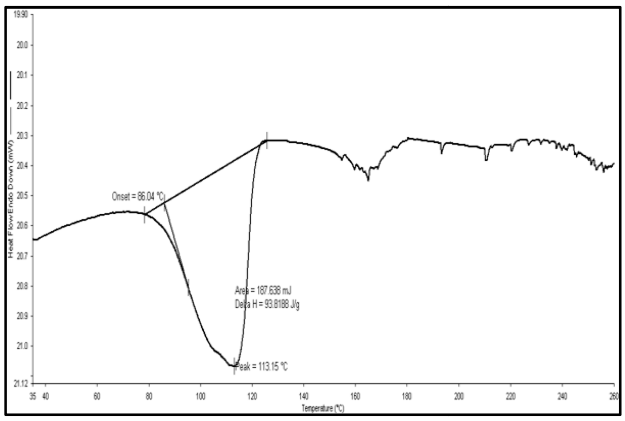

Fig 4e DSC thermogram of SB-TTDPM

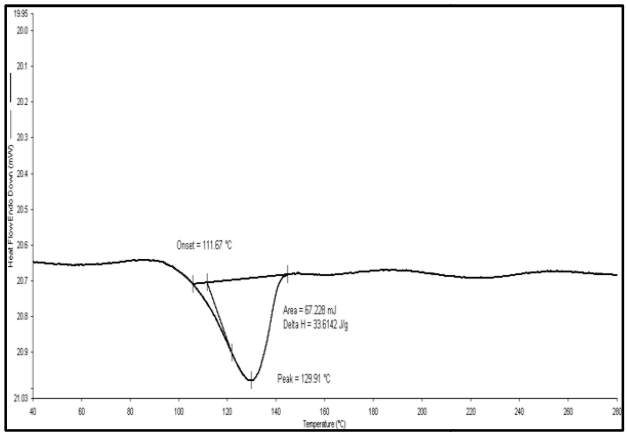

Fig 4f DSC thermogram of SB-TTDBM

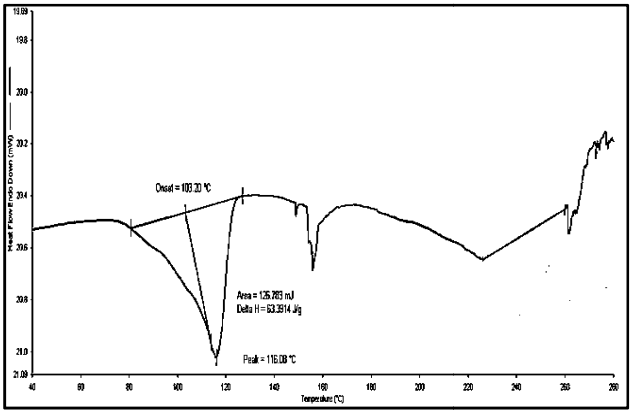

Fig 4g DSC thermogram of SB-TTDHM

sss

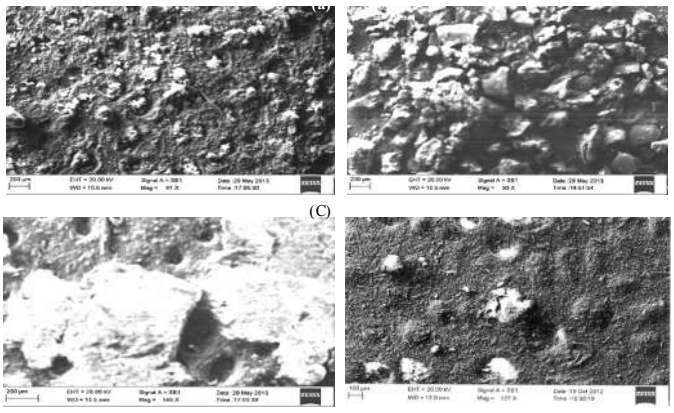

Fig 5 Surface morphology of (a) TTDPM, (b) TTDBM, (c) TTDHM, (d) SB, (e) SB-TTDPM, (f) SB-TTDBM and (g) SB-TTDHM

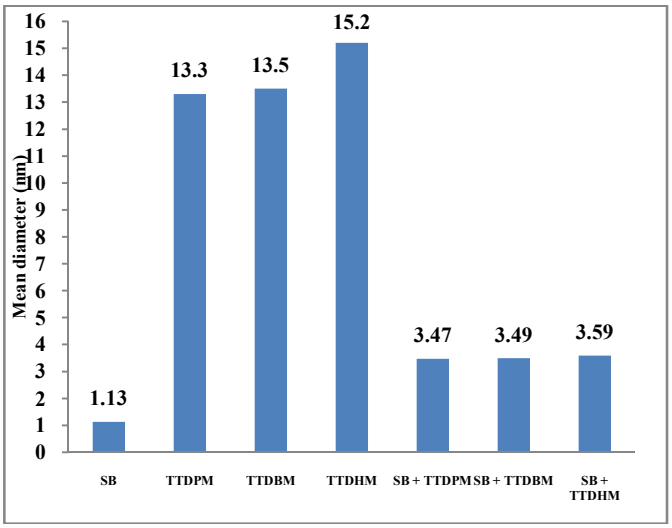

Fig 6 The mean diameter (nm) of SB, dendrimers and SB-dendrimer complexes

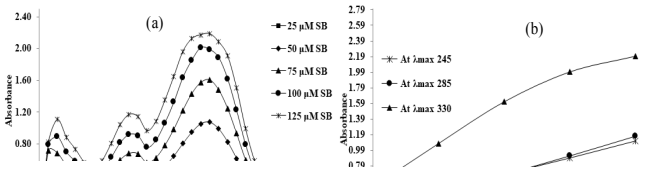

Fig 7 (a) UV-vis absorbance spectra of SB, (b)Standard absorbance calibration curve of SB at λ_{max} 245, 285 and 330 nm

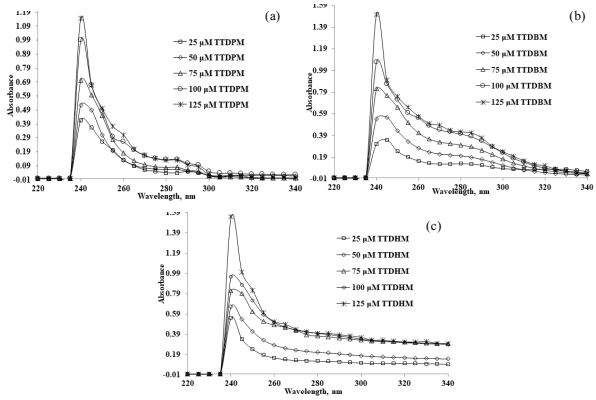

Fig 8 UV-vis absorbance spectra of (a) TTDPM, (b) TTDBM, and (c) TTDHM

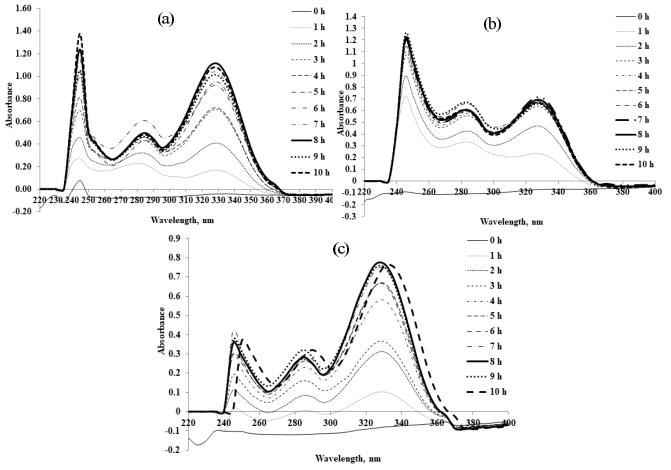

Fig 9 UV-vis absorbance spectra of (a) SB-TTDPM, (b) SB-TTDBM, and (c) SB-TTDHM

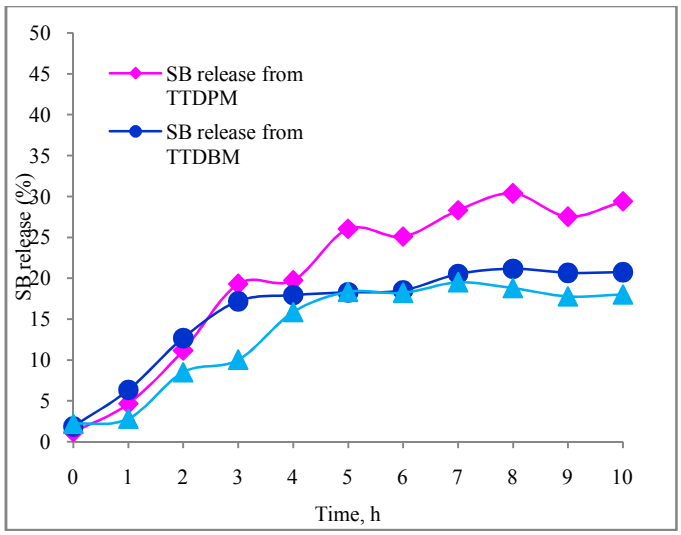

Fig 10 Comparative release profile of SB from TTDPM, TTDBM and TTDHM

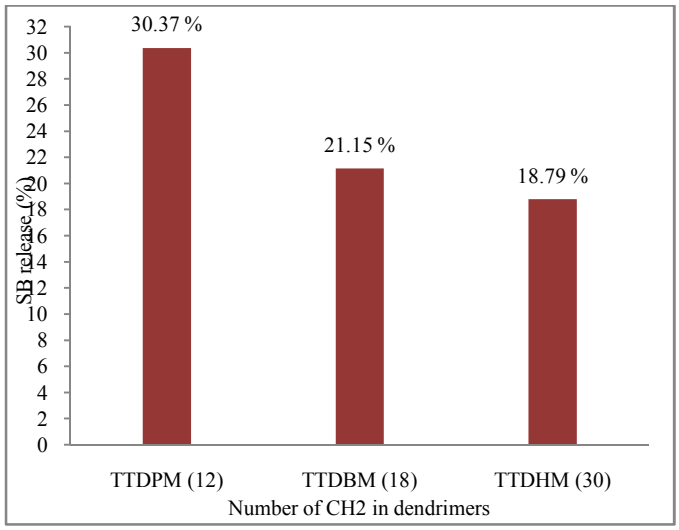

Fig 11 The -CH_2 activities for SB release (%) from TTDPM, TTDBM and TTDHM

Table 1 Mean diameter (MD, nm) and polydispersity index (PDI) of TTDPM, TTDBM and TTDHM, SB + TTDPM, SB + TTDBM and SB + TTDHM.

Sample	MD	PDI
TTDPM	13.30	0.0117
TTDBM	13.50	0.0128
TTDHM	15.20	0.0178
SB	01.13	0.0713
SB + TTDPM	03.47	1.1803
SB + TTDBM	03.49	1.1834
SB + TTDHM	03.59	1.1958

Table 2 Absorbance of pure SB, TTDPM, TTDBM and TTDHM concentration (µM) in phosphate buffer saline with 10 % DMSO

µM	TTDPM	TTDBM	TTDHM	SB		
		240 nm		245 nm	285 nm	330 nm
25	0.417	0.313	0.552	0.242	0.224	0.518
50	0.526	0.544	0.663	0.465	0.454	1.074
75	0.704	0.820	0.818	0.682	0.678	1.606
100	0.989	1.068	0.958	0.890	0.918	1.987
125	1.146	1.507	1.545	1.107	1.170	2.187

Table 3 Absorbance values of SB released at 0 to 10 h from SB + TTDPM, SB + TTDBM and SB + TTDHM complexes at λ_{max} 245, 285 and 330 nm in phosphate buffer saline with 10 % DMSO.

h	SB + TTDPM			SB + TTDBM			SB + TTDHM		
	245	285	330	245	285	330	245	285	330
0	0.073	-0.072	-0.043	-0.089	-0.105	-0.068	-0.102	-0.118	-0.080
1	0.272	0.219	0.169	0.721	0.333	0.231	0.015	0.007	0.103
2	0.458	0.318	0.407	0.890	0.426	0.462	0.109	0.083	0.310
3	0.698	0.432	0.703	1.058	0.555	0.626	0.188	0.162	0.365
4	0.812	0.461	0.719	1.089	0.573	0.654	0.290	0.229	0.578
5	1.039	0.433	0.949	1.128	0.591	0.666	0.358	0.263	0.668
6	1.148	0.610	0.915	1.199	0.657	0.675	0.300	0.273	0.663
7	0.988	0.501	1.032	1.190	0.589	0.748	0.414	0.291	0.710
8	1.235	0.497	1.107	1.205	0.603	0.771	0.352	0.283	0.685
9	1.050	0.464	1.003	1.240	0.666	0.753	0.372	0.320	0.648
10	1.379	0.486	1.072	1.178	0.599	0.756	0.367	0.321	0.657

Table 4 The SB release (%) at 0 to 10 h from the TTDPM, TTDBM and TTDHM dendrimers in phosphate buffer saline with 10 % DMSO at 37 ^{0}C at λ_{max} 330 nm.

h	TTDPM	TTDBM	TTDHM
	SB release (%)		
0	01.18	01.87	02.19
1	04.64	06.34	02.83
2	11.17	12.67	08.50
3	19.29	17.17	10.01
4	19.73	17.94	15.86
5	26.04	18.27	18.33
6	25.10	18.52	18.19
7	28.31	20.52	19.48
8	30.37	21.15	18.79
9	27.52	20.66	17.78
10	29.41	20.74	18.02

DSC

DSC analysis shows that all dendrimers, SB and their corresponding complexes show one endotherm in their respective thermograms that have characteristic peaks located at 261.17, 240.16, 213.00 and 158.16 ^{0}C for TTDPM, TTDBM, TTDHM and SB respectively (Figs. 4a-4f). The MPs were found to vary as 229.14> 227.83> 198.42 >145.66 ^{0}C for TTDHM > TTDBM > TTDPM > SB and attributed to an onset of MP with a characteristic phase formation. Higher MPs value by 1.31 and 30.72^{0}C of TTDHM as compared to TTDBM and TTDPM dendrimers have inferred the presence of an additional covalent bond of -CH_2 in TTDHM. The -CH_2 induced hydrophobic interactions through stronger covalent forces and

the prevalence of an induction effect, a factor for interaction with an electron releasing capacity of the terminal $-CH_3$ in TTDHM is noticed. The electron releasing capacity of $-CH_3$ is disrupted by $-CH_2$thereby resulting in lowering MP of TTDPM and TTDBM as compared to that in case of TTDHM. Variations in ΔH, area, onset and FTIR of the dendrimers prove and underline an effect of $-CH_2$ activities. The SB-TTDPM, SB-TTDBM and SB-TTDHM complexes show one endotherm in their DSC thermograms and exhibited one endotherm less than a melting peak of SB (Figs. 4e-4g). The encapsulation of SB in interstices of dendrimers resulted in shifting of peaks to a lower MP at 113.15, 129.91 and 116.08 ^{0}C region as compared to those of pure dendrimers and SB.Furthermore, the endotherm of dendrimers and SB corresponds to their melting that was not observed in case of SB-dendrimer complexes. An absence of SB melting endotherm in complexes suggests that SB is encapsulated in dendrimers and is prevalent the carriers.

Morphological study

The investigation of dendrimers through SEM micrographs showsan almost equal distribution of molecular geometries with longer, threadlike structures that are branched and distributed with almost different sizes (Figs. 5a-5c).In comparison to TTDPM, the TTDBM has shown a denser structure but the TTDHM has developed a thicker and compact structure with their homogeneous distribution. In case of TTDPM, smaller sized and shaped structures appear to be sparingly distributed with smaller surface areas.Thus, the TTDHM has developed a closely packed structure as compared to TTDPM and TTDBM which is confirmed by a higher PDI value that is by 0.0061 with almost uniform distribution (Table 1). Dissimilarity in SEM images of dendrimers clearly establishes the impact of elongation of dialkyl malonate chain. In case of SB-dendrimers complex the encapsulation of SB has resulted in the induction of remarkable changes in the surface morphology of dendrimersas proven by their FTIR, DSC and DLSstudies. The dendrimers and SB have formed aggregates that were almost spherical shown in SEM micrographs (Figs. 5d-5g). Small and spherical aggregates of SB with dendrimers showed a 3D network conformation composed of dialkyl chain length, driven by concurrent involvement of HB and hydrophobic interactions. However, the SB has shown a globular type SEM image with larger sized clusters occupying almost equal bulk area,which shows that the solid, SBexists as clusters of different geometries may be due to many benzene rings with many 5-OH groups whose activities are monitored through their motions (Fig. 1). A comparativedistribution of SB with TTDHM inferred that the interstices of TTDHM are most effective locations for holding and accommodating the SB. As compared to the internal morphology of SB-TTDPM and SB-TTDBM, the SB is closely bound with TTDHM due to the $-CH_2$ activities where the $-CH_2$could act as a rider on structural and functional behaviour of TTDHM. However,a compact structure of SB + TTDHM depicts a surrounding around SB which formsspherical structures as compared to that in TTDPM and TTDBM. Thus, the highly tentropyand IMMFT play a critical role in enhancing SB binding in the respective complexes.

Mean Diameter and Polydispersity Index

The mean diameter (MD) and polydispersity index (PDI) results have suggested about the aggregation behavior of dendrimers and SB-dendrimers complexes in Tween 60 as dispersion medium. The MD values were found 13.30, 13.50, 15.20 and 3.47 nm for TTDPM, TTDBM, TTDHM and SB respectively (Fig. 6 and Table 1). The highly branched and spherical structural morphology of dendrimers shows higher MD values than those of SB alone. The additional -CH2 activities with hydrophobicity in TTDHM imply a higher MD as compared to TTDPM and TTDBM proven in FTIR study. The MD of the complex aggregation ranged from 3.47, 0.349 and 3.59 nm for SB + TTDPM, SB + TTDBM and SB + TTDHM respectively. The DLS data also shows a slightly lower MD and higher PDI from 13.30 to 0.59 nm and 0.00117 to 1.1958 upon getting complexed with SB on effective aggregation in Tween 60 dispersion medium which clearly infers an involvement of HB and hydrophobic interactions (Fig. 6 and Table 1). It is interesting that the formation of SB–dendrimers complex has been highly ordered and reoriented towards variable dialkyl malonate branches of dendrimers responsible for the hyper-branched complex formation and moderated by interstices of a tree-like architecture of individual dendrimers. The dendrimers and complexes were not uniform in size as indicated by the MD and high PDIinferred that homogeneous distribution of SB without any evidence of the presence of any collapsed particles in interstices of TTDPM, TTDBM and TTDHM.

In vitro SB Release from Dendrimers

Characterization through FTIR, DSC, DLS and SEM of TTDPM, TTDBM and TTDHM dendrimers have showna good capacity to encapsulate SB. Encapsulation was purely based on HB interactions responsible for binding and releasing activities for the SB. The SB in PD solution gives maximum absorbance in the UV region at its characteristic wavelength found at 245, 285 and 330 nm (Fig.7a and Table 2). At 245, 285 and 330 nm the absorbance increases with increasing concentration of SB and at 125μM the absorbance values are 1.107, 1.170 and 2.187 respectively (Fig. 7a and Table 2). A calibration curve of SB was obtained for 25, 50, 75, 100 and 125 μM SB (Fig. 7b). Similarly, the 25, 50, 75, 100 and 125 μM of TTDPM, TTDBM and TTDHM were separately dissolved in PD solution and found 1.146, 1.507 and 1.545 absorbance at 240 nm respectively (Figs. 8a-8c and Table 2). The increase in absorbance values inferred an impact of $-CH_2$ in respective dendrimers. Since dendrimers in the PD solutions produce absorbance at 245, 285 and 330 nm, the absorbance obtained from SB-dendrimer solution belongs to SB (Figs. 9a-9c and Table 3). This absorbance was correlated to a calibration curve for determining amount of SB. In vitro release of SB from TTDPM, TTDBM and TTDHM dendrimers have observed a sustainable process with an initial release monitored by a slow release (Fig. 10 and Table 4). However, significant release of SB in present study was slower. A release profile of SB has inferred a higher solubility in PD (pH 7.4, 37 0C) as compared to that of water. The release was significantly slowed down to 18.79, 21.15 and 30.37% of SB, being released after 8 h from TTDHM, TTDBM and TTDPM and respectively (Fig. 10 and Table 4). The SB release strongly moderated by interstices of

dendrimers and interestingly was observed that increasing number of -CH_2 in respective dendrimers is decreased a release activities profile (Fig. 11).It has inferred a development of HB and hydrophobic interactions of SB are major mechanisms of encapsulation. Interestingly, an increase in number of dialkyl malonates branches and a size of internal voids were shown to enhance an encapsulation of SB. On the other hand, the number of -CH_2 groups in dipropyl malonate ester as branching units of TTDPM dendrimer had shown slightly reduced binding capacity with higher SB release capacity as compared to TTDBM and TTDHM. Stronger binding and weaker releasing activities of SB with dendrimers have inferred a development of stronger hydrophobic forces depicted by FTIR (Figs. 3a-3g). Thus,a reduced SB release is beneficial for controlling a release rate in drug delivery system. These significant results have suggested that HB and hydrophobic interaction have developed anintramolecular multiple force for encapsulated of SB in TTDPM, TTDBM and TTDHM with major effect on its release activities.

CONCLUSION

Drug-dendrimer complexes based on SB and a series of variable dialkyl (dipropyl to dihexyl) malonate ester terminated 1st tier dendrimers were characterized by using FTIR, DSC, DLS and SEM. These studies have inferred that TTDPM, TTDBM and TTDHM could be considered as a potential SB carrier. The UV Vis analysis showed a sustained release behavior of SB from these dendrimers under prescribed conditions. The encapsulation of SB into the dendritic structures strongly depends on the variable dialkyl chain activities in TTDPM, TTDBM and TTDHM which could be applied in controlled release drug delivery systems and beneficial in biomedical sciences.Hence, it may be concluded that the series of variable dialkyl malonate chain signifies an important factor which may enhance the binding and releasing activities of SBwith TTDPM, TTDBM and TTDHM dendrimers. Studies on TTDPM, TTDBM and TTDHM with variable lengths of dialkyl chain have revealed that these are noteworthy and potential drug carriers for SB with a controlled and sustained release tendency.

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