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Effects of Non-covalent interactions of Methotrexate to a series of 1st tier Dendrimer On its Binding and Breast cancerous cells for Toxicological estimation

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ABSTRACT

A study of 1st tier Dendrimer series (Trimesoyl 1,3,5-tridialkyl malonate ester: TTDAM) as drug delivery vehicle encapsulated with the model drug (Methotrexate: MTX) individually, for breast cancer drug delivery and in vitro evaluation of toxicity of serial dendrimers with their complexes on the breast cancer cell line suggesting new awareness for developing safe breast cancer drug delivery system. MTX-TTDAMs were prepared using a 1 : 1 ratio of MTX and TTDAM, in acetone medium at RT followed by 24 h. MTX-TTDAMs formed by hydrogen bonding confirmed through FTIR and further characterized by SEM and DLS for their morphological and narrow particle size distribution (on nm scale) respectively. The –OH stretching frequency at 3356.2, 3352.5, 3420 and 3416.3 cm-1 for MTX, MTX-TTDMM, MTX-TTDEM and MTX-TTDPM, respectively absent in dendrimer series elucidating weak hydrogen bonding between –OH and ester group. A strong stretching of amide at 1648.2 cm-1 in MTX, remains at same position in MTX-TTDMM and MTX-TTDEM aspect MTX-TTDPM shows amide stretching at 1640.7 cm-1, confirms impact of amide group in binding. MTX-TTDPM illustrated less number of aggregates due to more binding of MTX with TTDPM and rest self-aggregate such as molecular self-assembly. Trimesoyl 1, 3, 5-tridimethyl malonate ester (TTDMM), trimesoyl 1, 3, 5-tridiethyl malonate ester (TTDEM) and trimesoyl 1, 3, 5-tridipropyl malonate ester (TTDPM) has void spaces and functionality which assistances to bind MTX anticancer drugs for their impending use in breast cancer drug delivery system. The higher hydrophobicity of TTDPM errands more methotrexate binding and controlled release profiles compared to TTDMM and TTDEM. Effects of dendrimers and their complexes were tested on cell viability by SRB assay using a human breast cancer cell line (MCF-7), remarkably inhibits the growth of MCF-7 breast cancer cells.

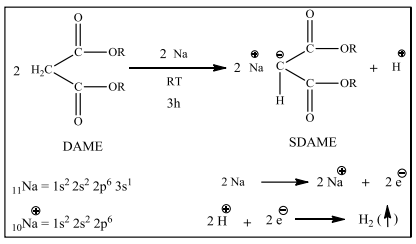
INTRODUCTION

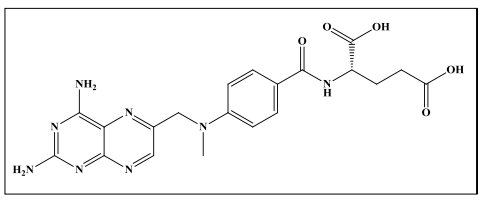
Dendrimers have been widely used in drug delivery system and developed as new vehicles in biomedical and biochemical sciences by reducing side effects of drug and providing safer drug binding and release without any structural deformities due to their unequaled properties.

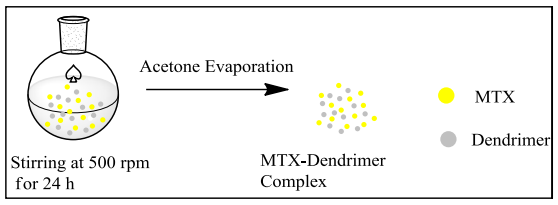
We proposed a highly efficient dendrimer-MTX delivery system for transdermal delivery, may be a promising delivery system for MTX with high solubility, bioavailability, biocompatibility, lesser side effects and improved skin permeation of poorly water soluble MTX with controlled release characteristics.

METHODOLOGY

- Synthesis of dendrimers (TTDMM, TTDEM and TTDPM)
- Synthesis of MTX-Dendrimer Complexes

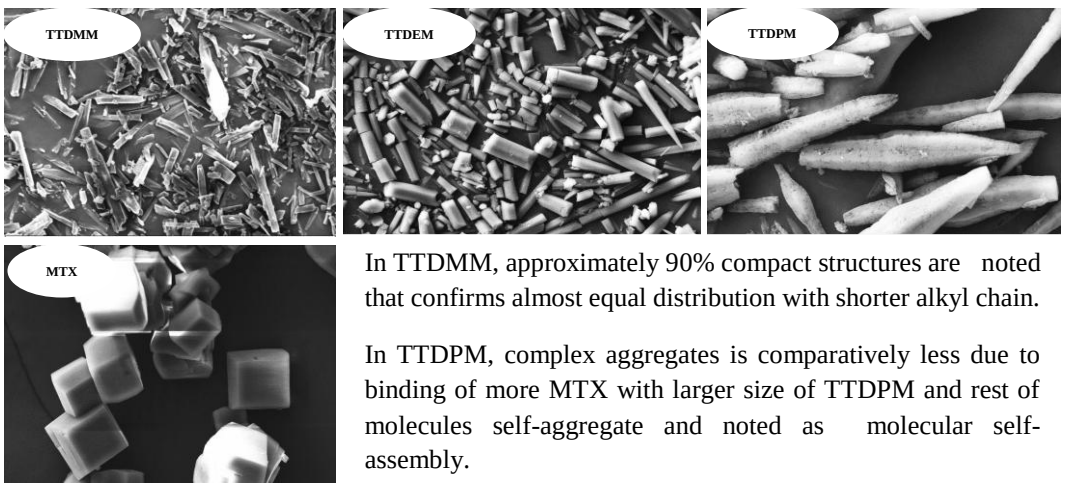






Study of *in-vitro* MTX release from MTX-Dendrimers Complex via UV-vis Spectroscopy

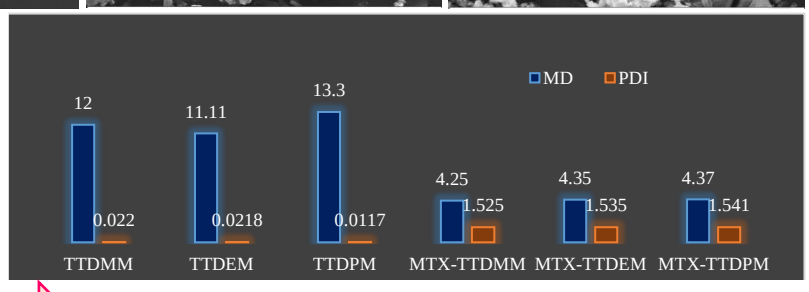
RESULTS



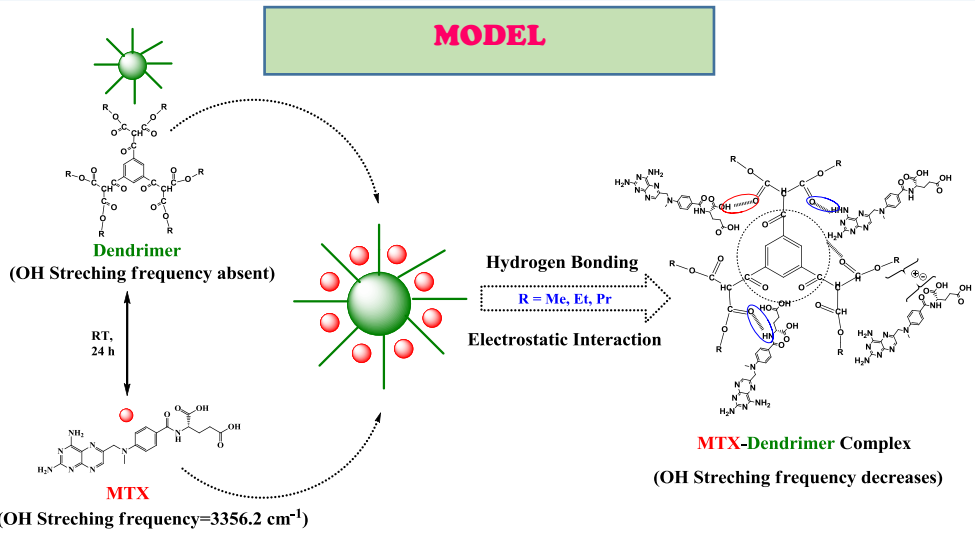
In TTDMM, approximately 90% compact structures are noted that confirms almost equal distribution with shorter alkyl chain.

In TTDPM, complex aggregates is comparatively less due to binding of more MTX with larger size of TTDPM and rest of molecules self-aggregate and noted as molecular self-assembly.

Decrease in the size of complexes shows formation of complex and its more compact structure.



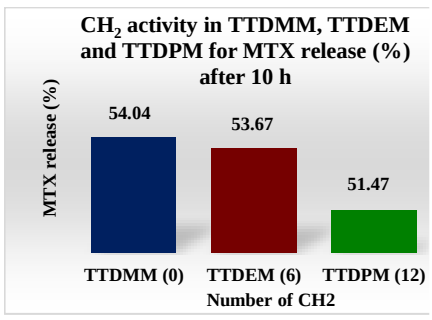
MODEL



System	CO	C=C	System	OH/NH	CO	C=C	CO-NH
TTDMM	1735	1618.4	MTX-TTDMM	3352.5	1734.5	1606.9	1648.2
TTDEM	1728.6	1608	MTX-TTDEM	3420	1723.3	1603.1	1648.2
TTDPM	1732.2	1622.4	MTX-TTDPM	3416.3	1727	1606.9	1640.7
			MTX	3356.2			1648.2

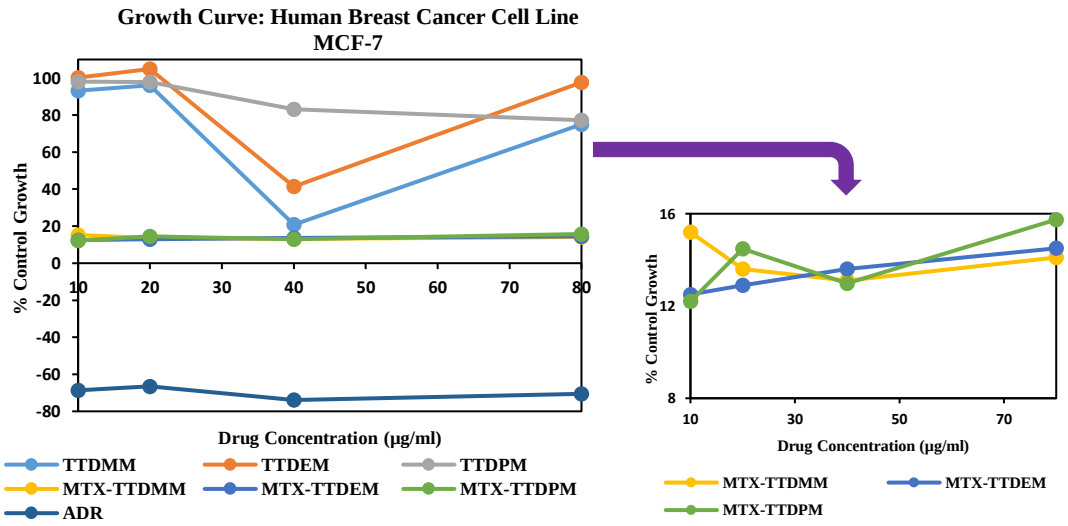
- MTX form complexes through weak physicochemical forces between –OH/–NH and ester group. More decrease in frequency with TTDPM indicates a higher and stronger MTX binding with longer alkyl chain.
- >CO of amide group and confined fingerprint region in complexes also show MTX binding. C=C stretching of core also involves due to an additional stress on C=C of the core.

In-vitro release



- The MTX release is biphasic with initial quick release followed by a slow release.
- The quick release is reduced with an increasing alkyl chains at the outer surface reducing diffusion of drug because MTX released from TTDMM is higher, implied that MTX is strongly held by TTDEM and TTDPM.
- Due to this, dendrimers have the potential to control the release of drug.

SRB Assay



Increase the length of alkyl chain of dendrimer strengthens their hydrophobicity and hence the most hydrophobic constituents of DNA could initiate stronger hydrophobic interactions with hydrophobic part of dendrimer like TTDPM. Such phobic-phobic mechanism could damage cancer cell line DNA structure to a level where it could not replicate or multiply.

CONCLUSION

MTX with TTDPM dendrimer is a highly promising and sustainable delivery system for drugs and will be further investigated *in-vivo* to optimize its therapeutic potential.

REFERENCES

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