WWW.IJRPR.COM

International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

Reversible Addition Fragmentation Chain Transfer (RAFT) Polymerization: A Metal Free Methodology to Prepare Graft Copolymer.

Mwikwm Basumatary

Department of Chemistry, Gossaigaon College Gossaigaon, Gossaigaon-783360, BTR, Assam, India.

ABSTRACT:

Reversible Addition Fragmentation Chain Transfer (RAFT) polymerization is one of the most successful method employed for the synthesis of graft copolymers with well-defined architectures and good control over molecular weight distribution and polydispersity. This study reviews the grafting of various monomers including acrylates, vinyl monomers, etc via RAFT polymerization onto the surface of polymers and biopolymers including cellulose, lignin, starch, chitosan under metal free considerations. This review explores on various methods such as Diels-Alder cycloadditon, click chemistry, enzymes mediated such HRP/ACAC/H2O2 system , **γ**-irradiation based and PET based RAFT processes that are being used to yield the best results for the synthesize of graft copolymers.

Keywords :

- **Controlled Radical Polymerization**
- **Click chemistry**
- **Mitoxantrone**
- **Graft copolymer**
- **PBA**
- **PMMA**
- **PEG**

1.0 INTRODUCTION:

RAFT polymerization is one of the three main types of the controlled radical polymerization(CRP) others being ATRP(atom transfer radical polymerization) and NMP(Nitroxide-mediated polymerization). RAFT is a versatile method to carry out polymerization of monomers such as styrenes, acrylates, acrylamides, butadiene and many vinyl monomers. RAFT method allows synthesis of varied well-defined polymers including- block, gradient, cross-linked networks, star polymers and also more complex architectures including microgels and polymer brushes.[1,2] The advantages of RAFT polymerization includes:

- The ability to control polymerization of most monomers which are polymerizable by radical polymerization such monomers include methacrylates, (meth)acrylamides, styrenes,dienes, vinyl acetates, vinyl pyrrolidone, vinyl esters etc.
- Tolerance to vulnerable functionality in monomers and solvents.The polymerization can be carried out both in aqueous or protic solvents.
- Wide scope of reaction conditions(bulk,aqueous,emulsion,suspension) with ease performance and it is an inexpensive method.
- Easy and reliable synthesis of RAFT agent under mild reaction conditions.

The RAFT polymerization is carried out in presence of initiator or RAFT agents which are most commonly thiocarbonylthio groups. Some of the common RAFT agents that are being employed in polymerization includes Dithioesters, dithiocarbamates, trithiocarbonates, xanthates, dithiophosphonates etc.The use of proper RAFT agent for the polymerization of monomer results in well-defined polymer with controlled molecular weight and narrow polydispersity (close to 1).[1,2]

The general scheme of RAFT Polymerization is shown in fig: 1.1

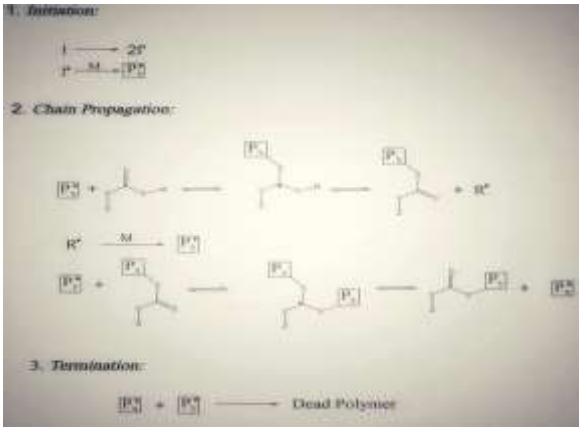

Fig: 1.1

1.1 GRAFT COPOLYMER:

It is a type of copolymer in which one or more blocks of homopolymer are grafted as branches onto the main polymer chain. The components of the side chain are structurally different than that of the main chain[1]. Grafting generally involves covalently bonded monomers onto the main chain[3].The grafting of a polymer can be carried out by three main techniques as discussed below:

i. Grafting onto- In this method a polymer chain consisting of randomly distributed functional groups on its backbone undergoes coupling reaction with the other polymeric chain having reactive group at its end.[1] This type of method can be obtained by application of well suited click chemistry. The method is employed for synthesis of star molecules and loosely grafted copolymers.[4]

ii. Grafting from- In this method the polymer backbone is first modified with certain other monomers consisting of functionalities. The monomers present in this polymeric main chain thus initiates further polymerization with the desired monomers resulting in graft copolymer.[1,4]

iii. Grafting through- In this method monomers with low molecular weight are copolymerized by macromonomers that consist of functionalized groups at its end. Some of these end groups includes polyethylene, polyethylene oxide, polysiloxanes, polycaprolactone etc incorporated into the polystyrene or PMA backbone. This method is desirable for the synthesis of well-defined side chains with controlled polydispersity.[7].

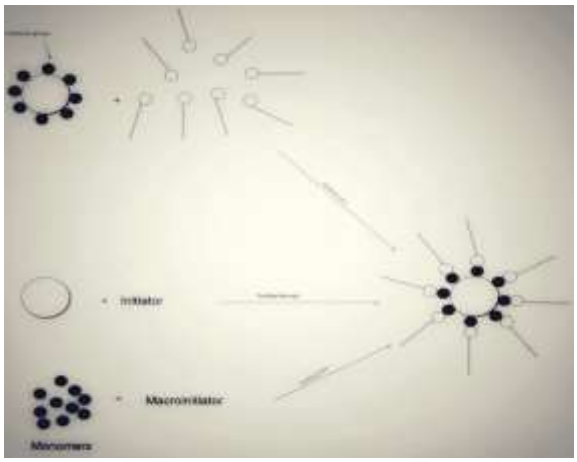

Fig: 1.2

2.0 LITERATURE REVIEW:

2.1

Grafting onto method was employed to prepare bottlebrush polymers under metal free environment by combining RAFT and Triazolinedione-diene click reaction. Triazolinedione (TAD) molecules are heterocyclic azide compounds that consist of two carbonyl functionalities, they are also known as urazole derivatives. TAD compounds are employed for ultra fast Diels-Alder and ene type reactions. The compound can effectively be used for covalent cross-linking in dynamic polymeric systems without any necessity of catalyst.TAD(Triazolinediones) can reversibly undergo click reaction with ene groups, click chemistry of indole with TAD has been extensively studied and observed, TAD-indole adduct so formed as the product by the reaction of TAD with

indole containing substrate allows click reaction which can effectively link macromolecular chains at room temperature within minutes,on further reaction with the reversible adduct with Diels-Alder reaction partners it results in formation of new irreversible Diels-Alder adduct.[6]

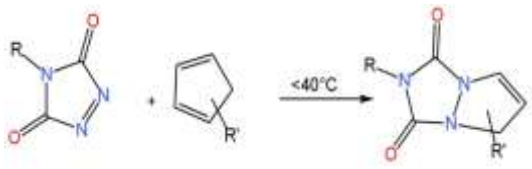

Fig: 2.1

Xiao et al.(2016) performed the grafting onto method to prepare bottle brush polymers employing the TAD-diene ultrafast Diels-Alder cycloaddition reaction, click chemistry. The polymer backbone and side chains were prepared separately and then highly efficient coupling reactions was carried out to connect them together to give well-grafted bottlebrush polymers. Their studies revealed the grafting efficiencies for TAD- terminated polymer side chains for poly(methyl methacrylate) (PMMA), poly(tert-butyl acrylate) (PtBA) and polystyrene(PS) onto the polyacrylate backbone PHEA or poly(2-Hydroxyethyl acrylate). The coupling reaction was performed between PHEA-diene (polymer backbone) and TAD-PMMA side chains. The net grafting scheme can be understood from fig 2.2

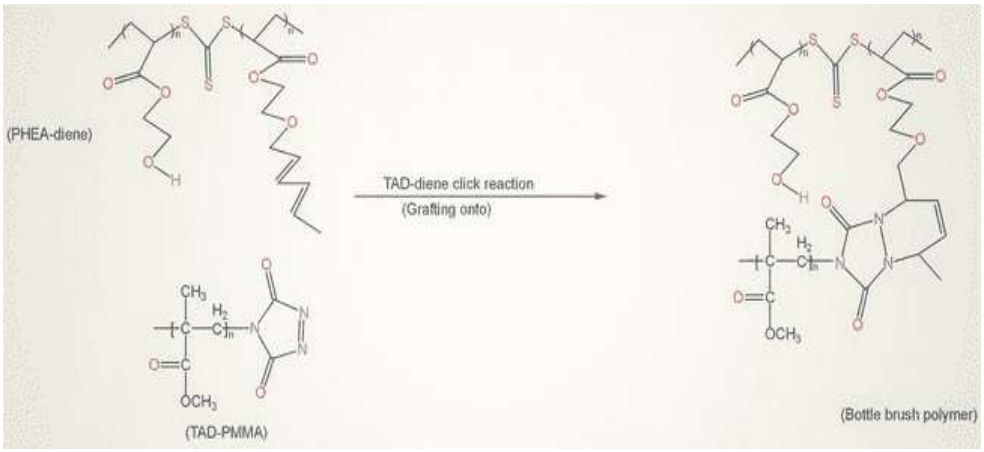

Fig: 2.2

Initially a RAFT agent: Urazole CTA-1 was synthesize,from which Urazole terminated PMMA was prepared, the TAD-PMMA (side chains) was then obtained by dissolving Urazole-PMMA in DABCO-Br solution in presence of $CHCl_3$. PHEA diene polymer backbone which was synthesized is then grafted with TAD-terminated polymer chain(TAD-PMMA).Their reports suggested that grafting for TAD-PMMA side chains had achieved graft density of about 85% within a 5 minutes of time which increased further to 90% or above only after 10 minutes.Similar experiments of TAD-diene coupling reaction was adopted for P*t*BA and PS side chains there results suggested that the grafting densities could reach to 90% only after 1 minute of coupling reaction which could further increase to 95% within 10 minutes.[5]

The experiments conducted by Xiao and his coworkers strongly suggested that TADdiene based click chemistry as employed for polymerization of PMMA,P*t*BA and PS side chains can be a versatile tool for the preparation of many highly dense bottlebrush polymers via grafting onto approach without any need of metal or a catalyst within a very short time.The initial to the final scheme for the grafting process using RAFT agent(Urazole-CTA1) as adopted by Xiao & his coworkers can be pictorially summarized as shown in fig: 2.3

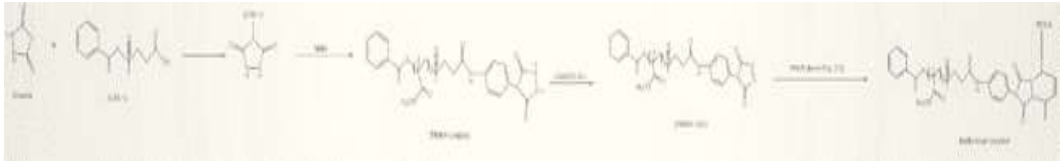

Fig : 2.3

2.2

Zhang et al.(2013) reported the synthesis of dual stimuli responsive grafted chitosan copolymer via the route of RAFT polymerization[10].Chitosan a versatile biopolymer serves as a polymeric backbone for the grafting of poly(N-isopropylacrylamide)-block-poly(acrylic acid) (PNIPAM-b-PAA) branched chains.[10] Initially chitosan was modified using o-phthalic anhydride to obtain N-phthaloylchitosan, which is then further modified by BPATT (3-benzylsulfanyl thiocarbonylsulfanyl propionic acid) an asymmetric trithiocarbonate compound known for its uses as CTA.The N-phthaloylchitosan-

BPATT(CTA) compound so obtained was further grafted with PAA(polyacrylic acid) to obtain N-phthaloylchitosan-g-PAA,this compound is then further polymerized with PNIPAM in DMF to obtained the main graft copolymer that is N-phthaloylchitosan-g-(PNIPAM-b-PAA).The overall synthesis route is shown in fig: 2.4

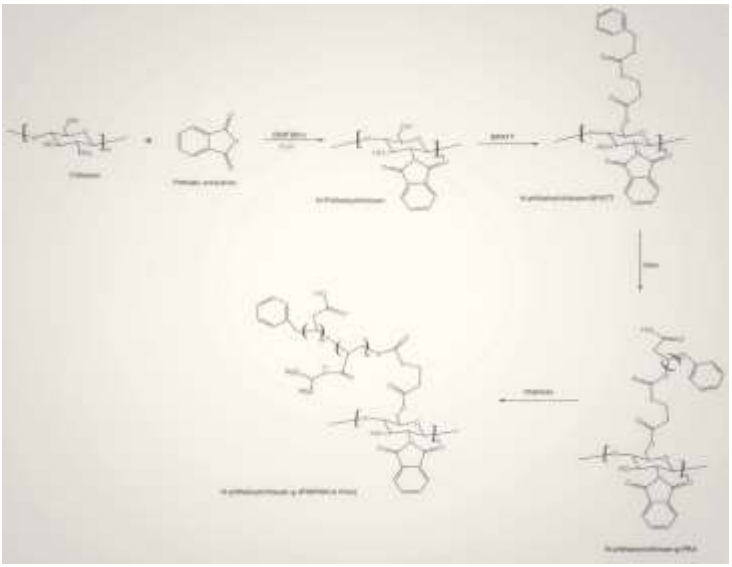

Fig: 2.4

One of the major drawbacks could be in the synthesis of N-phthaloylchitosan-BPATT which is obtained via esterification of N-phthaloylchitosan and BPATT resulted only 68% of subtitution of BPATT arising as a result of steric hindrance thus,the overall substitution is possible only at C_6 position this clearly suggested that the esterification followed the regioselective substitutions and so there is no scope of further modifications of substitutions at any other positions of N-phthaloylchitosan.

2.3

Bao et al.(2019) reported the modification of lignin by "grafting to" approach employing the enzyme initiated RAFT polymerization. Lignin is a heterogeneous high molecular weight insoluble plant polymers and exist as the second most abundant biopolymer in nature after cellulose.[13] Lignin consist of phenyl propane units and it fills out the cell walls of plants providing structural rigidity.The primary building units of lignin are cinnamyl alcohols,coniferyl,sinapyl alcohol and p-coumaryl alcohol[14].Xueming Bao and his fellow coworkers reported surface modification of lignin with different vinyl monomers(AM and BA) by RAFT polymerization using HRP/ ACAC/H_2O_2 system (HRP- Horseradish peroxidase, ACAC- acetyl acetone).[12] HRP and H_2O_2 complex catalyzed the oxidation of ACAC to yield free radicals which initiated the RAFT polymerization for AM and BA.[12] PAM and PBA synthesized were then incorporated to the phenolic radicals on lignin giving modified grafted polymers lignin-g-PAM and lignin-g-PBA. Because of broad molecular weight distribution of raw lignin and uncontrollable grafting density the PDI values are still relatively high for modified lignins.

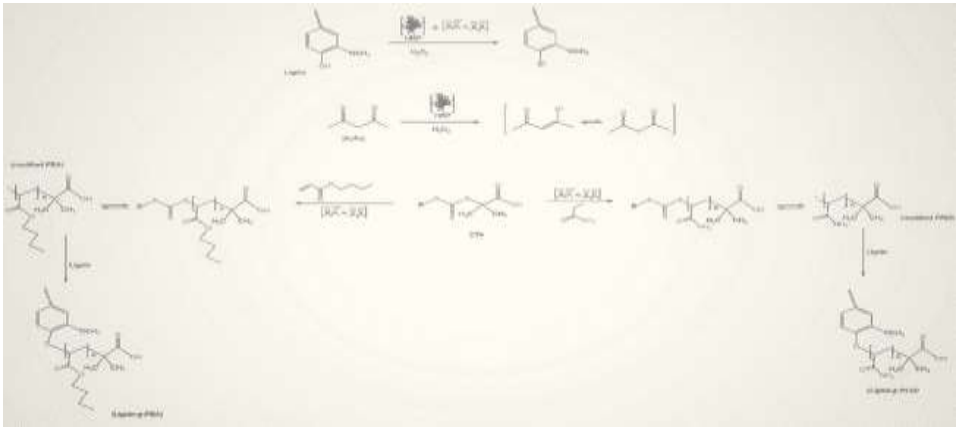

Fig: 2.5

2.4

Feng et al.(2021) reported a unique way of modifying a hydrophobic drug mitoxantrone(MTX) via grafting onto it the poly(PEG-A) and then employing RAFT polymerization to obtained modified drug/polymer conjugate MTX/PPEG-A. Mitoxantrone is an anti-cancer or anti-neoplastic chemotherapy drug used to treat certain types of cancer including solid tumor, leukemia, lymphoma etc. The basic mechanism of this drug involves intercalation with DNA that causes disruption of single and double-strands of DNA and then inhibition of enzyme topoisomerase II that suppresses DNA repair.[16]

It is an immune suppressor and imparts cytotoxicity.[17] Despite of such abilities, mitoxantrone has limited application owing to the fact that it shows poor water solubility. Zhonghang and his coworkers revealed that the modification of MTX by grafting onto it the PPEG-A followed by RAFT polymerization in situ leads to the synthesis of well-defined polymer conjugated drug (MTX/PPEG-A) which exhibits nearly 550% more water solubility compared to the unmodified MTX. Further, MTX/PPEG-A can be hydrolyzed by esterase to yield pristine MTX. In order to synthesize the modified polymer conjugate, initially they prepared a macro-RAFT agent which serves as CTA in RAFT polymerization of PEG-A. Macro-RAFT agent is synthesized via esterification of alcoholic hydroxyl group of MTX with carboxyl group of 4-cyano-4-ethyl-trithio pentanoic acid (CETP) to yield MTX-CETP macro-RAFT agent. Then PEG-A RAFT polymerization is carried out on MTX employing MTX-CETP as chain transfer agent.

There successful experiment on MTX drug has clearly indicated the importance and future scope of polymer science towards the development of new kinds of alternatives for hydrophobic drugs by grafting them with certain suitable polymers and also by used of Reversible Addition Fragmentation Chain Transfer(RAFT) polymerization, this can potentially find many applications in the field of medicine and pharmacology.

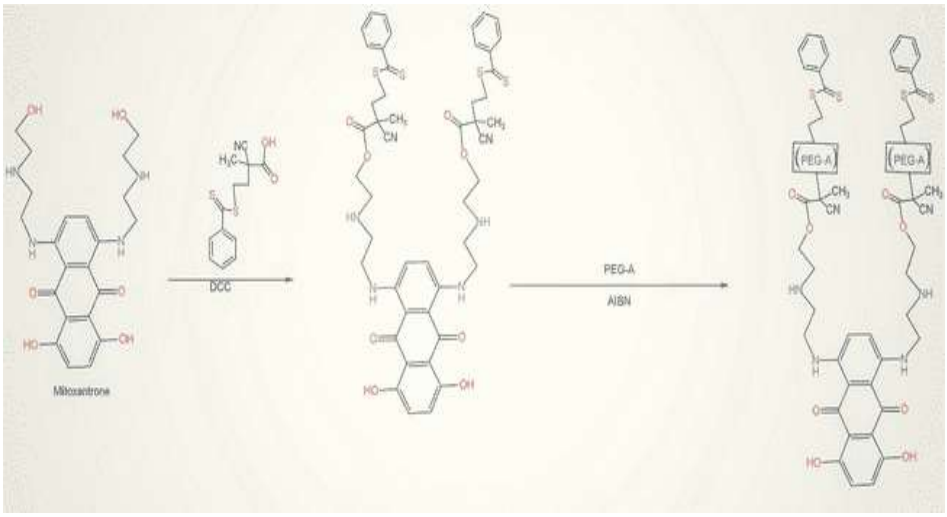

Fig: 2.6

2.5

Kodama et al.(2014) reported RAFT mediated free-radical copolymerization of 2-hydroxyethyl methacrylate (HEMA) onto cellulose fibers via "grafting-from" approach under γ-irradiation.[11] They used cumyl dithiobenzoate(CDB) as the RAFT agent, the grafting was carried out by introducing the cellulose films into a grafting solution containing monomer HEMA and CDB RAFT agent in a suitable solvent such as DMF. The solution was then subjected to the γ irradiation as carried out by Yasko and his coworkers then the final Cellulose-g-PHEMA copolymer was obtained. Although they were able to control the degree of grafting simply by changing the concentrations of [HEMA]/[CDB] ratio, they have also clearly cited the shortcomings in full control over molecular weight and the polydispersity as the γ-irradiation affected the PHEMA structure including branching or crosslinkings reactions. The overall grafting has an impact only at the surface of the cellulose and not to its bulk, their experiment also suggested that hydrophilicity of the grafted cellulose gradually decrease with the increase of grafting.[11]

2.6

Tucker et al.(2017) reported another method, that emphasizes modification of proteins, using grafting-from approach via metal-free photoinduced electron transfer-reversible addition fragmentation chain transfer(PET-RAFT) polymerization under mild visible light irradiation in presence of organo-photocatalyst including eosin Y.[8] Eosin Y is an acidic fluorescent xanthene compound used as dye.It is yellowish-red color with green fluorescence, the compound is often used as a counterstain in biological tissues.[9] Initially a modified CTA carrying lysozyme(LYS) was synthesized from a novel trithiocarbonate CTA bearing N-hydroxysuccinimidyl ester which is separated from trithiocarbonate moiety by a diethylene glycol unit as shown in fig 2.7 .[8]

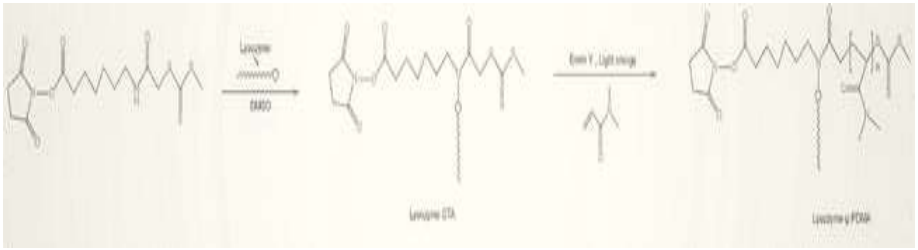

Fig: 2.7

The grafting-from polymerization of DMA(N,N-dimethylacrylamide) with LYS-CTA resulted nearly 92% of monomer conversion. There studies further revealed that monomer conversion and MW growth was observed only at high intensity light(blue wavelength), LYS-PDMA maintained 85±20% protein activity compared to unmodified LYS. They were also able to show similar polymerization for LYS-PHEA and LYS-PNaSS with 74% and 63% monomer conversion respectively, in 20hr.[8] Although there approach also clearly suggested the discrepancies of obtaining much higher MW of cleaved polymers during the process of cleavage of proteins from the polymer, which may lead to unexpected variations in chemical or physical properties of the polymer obtained.

2.7

Lu et al.(2011) reported the grafting of poly(vinyl acetate) onto starch through the RAFT polymerization. Starch owing to remarkable characters including biodegradability, low cost and renewability has been a good choice for developing various modified polymers till date.[15] A starch based RAFT agent (SCTA) is employed as the chain transfer agent to carry out controlled grafting of PVAc onto the starch backbone. The SCTA employed was starch-based xanthate agent, initially a starch is modified with bromoacetyl bromide to obtain a modified starch-bromide intermediate which on treatment with potassium ethyl xanthogenate in DMSO yield starch-based xanthogenate RAFT agent (SCTA) (yield:55%).The overall synthesis route for Starch-g-PVAc is shown in fig: 2.8

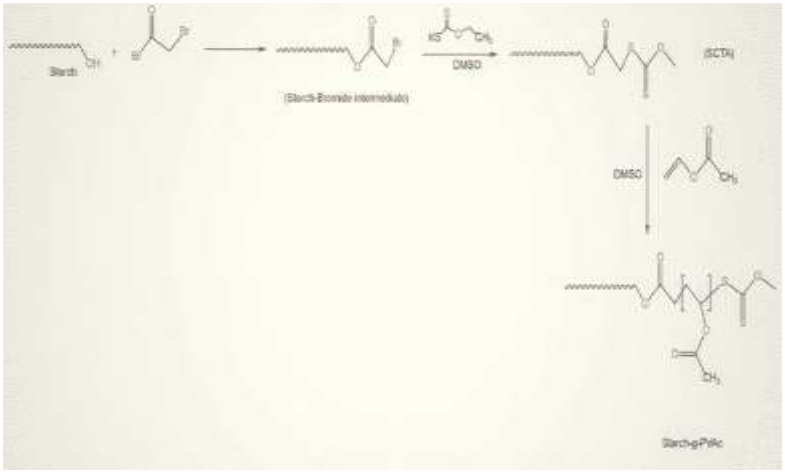

Fig 2.8

Their method suggested the versatility of SVAc possessing the property of self-assembly which reflects its amphiphilic nature and thus, RAFT polymerization reveals its scope for not just synthesis of well defined polymer architectures but also can serve as a successful tool for synthesis of functional micelles as well.

3.0 DISCUSSION:

The studies as discussed in our literature review suggest the wide varieties of grafting approaches onto a well-defined polymeric backbones including natural or biopolymers such as cellulose, starch, chitosan by employing RAFT polymerization as a powerful tool to achieved the successful products. The click chemistries of compound such as TAD-diene Diels-Alder cycloaddition reaction employed by Xiao et al.(2016) provides the potential synthetic route for preparation of bottle brush polymers without the need of any sort of metals or catalyst, the grafting densities which was 90% or even higher could be achieved within a few minutes of time, thus click chemistry seems to have bright scope in future for upcoming research area in polymer and material sciences. On the other hand achievement in grafting of proteins by employing enzymes carried out by PET(Photoinduced electron transfer) mediated RAFT polymerization as suggested by Tucker et al.(2017) sets a good example to synthesis various modified proteins which may have many biomedical applications indeed they have experimentally shown similar technique for synthesis of LYS-PDMA, LYS-PNaSS with above 60% monomer conversions, this clearly suggest that the method as adopted by them may find validity with many different functional monomers, however there must be

some alternatives needed to sort out discrepancies of obtaining higher MW polymer after the protein is being cleaved from its surface. Modification of chitosan via grafting with well defined PNIPAM-b-PAA branched chains to synthesize grafted chitosan(N-phthaloyl chitosan-g-PNIPAM-b-PAA) as presented by Zhang et al.(2013) reveals a new unique route of grafting via RAFT polymerization to prepare dual-stimuli hydrogels which can serve as potential drug delivery system with controlled release of drugs, however; there must be easier way to overcome the steric hindrance and regioselective substitutions during the grafting done by there method. We have also further seen in our review the modification of cellulose with 2-hydroxyethyl methacrylate(HEMA) by γ-irradiation. Cellulose-g-PHEMA copolymer was synthesized successfully, however, full control over the molecular weight and PD of the polymer couldn't be achieved, such shortcomings must be worked out to give desired products. Lignin a biopolymer that are found in plant cell wall is modified with acrylamide and butyl acrylate grafted onto its surface via HRP/ACAC/H2O2 catalyzed system mediated RAFT polymerization. Horseradish peroxidase that is HRP and H2O2 system is used to generate acetylacetone radicals that initiated the RAFT polymerization, thus lignin grafted lignin-g-PAM and lignin-g-PBA were successfully synthesized. This enzyme catalyzed method in modification of biopolymers such as lignin paved away a route to synthesize the compatible biomaterials. As already seen in our review,Lu et al.(2011) mentioned the successful grafting of starch with PVAc, that had a characteristic feature of amphiphilicity and thus RAFT method of polymerization can also be used for the synthesize of functional micelles. RAFT polymerization also has been successfully employed to synthesize modified drugs such as hydrophobic MTX(Mitoxantrone) grafted MTX-g-PPEG-A which showed significant water solubility compared to unmodified MTX. This therefore, shows the versatility of RAFT method of polymerization in various areas of grafting a polymer and impart them a new unique properties.

4.0 CONCLUSION:

RAFT polymerization is one of the most successful methods that has been employed for the synthesis of graft copolymers with remarkable properties. High compatibility, lower cost and its tolerance for wide range of monomers has made RAFT polymerization as one of the best controlled radical polymerization technique to be employed for polymerization, also the reactions can occur at milder conditions as compared to other CRP techniques, most RAFT agents are easy to synthesized and it is a promising tool to have control over molecular weight distributions and low PDI,RAFT polymerization process also provides large range of tolerance for solvents, this review has already revealed the versatility of RAFT polymerization in synthesizing materials which includes polymer-protein conjugates, polymer-drug conjugates, synthesis of micelles, enzyme-mediated such as those of HRP/ACAC/H_2O_2 reaction process etc. These facts suggest that the RAFT polymerization method has a huge scope in future.

ACKNOWLEDGEMENT:

For the successful accomplishment of this work I submit my humble regards to Dr. Drubhajyoti Haloi, Associate Professor, Bodoland University.

REFERENCES:

[1]. Graeme Moad, Ezio Rizzardo, San H.Thang: Radical addition fragmentation chemistry in polymer synthesis(2008)Polymer 49(5):1079-1131.

[2]. V Hasirci, P Yilgor, T Endogan, G Eke, and N Hasirci: Polymer fundamentals: polymer synthesis. (2011),Elsevier, Comprehensive Biomaterials (pp.349-371).

[3]. Hulya Arslan: Block and graft copolymerization by controlled/ living radical polymerization methods (2012) Edited by Ailton De Souza Gomes DOI: 10.5772/45970 .

[4] The Matyjaszewski polymer group> Graft copolymers. Carnegie Mellon University Department of Chemistry.

[5] Lifen Xiao, Yongming Chen and Ke Zhang: Efficient metal-free "grafting onto" method for bottlebrush polymers by combining RAFT and triazolinedionediene click reaction;(2016), Macromolecules 49(12):4452-4461.

[6]. Stijn Billiet, Kevin De Bruycker,Frank Driessen, Hannelore Goossens, Veronique Van Speybroeck, Johan M. Winne and Filip E.Du Prez: Triazolinediones enable ultrafast and reversible click chemistry for the design of dynamic polymer systems;(2014),Nature Chemistry volume 6, pages815–821

[7]. Uchida, S. (2013). Graft Copolymer Synthesis. In: Kobayashi, S., Müllen, K. (eds) Encyclopedia of Polymeric Nanomaterials. Springer, Berlin, Heidelberg. https://doi.org/10.1007/978-3-642-36199-9_185-1 .

[8]. Bryan S.Tucker, McKenzie L.Coughlin, C. Adrian Figg and Brent S. Sumerlin.Grafting-from proteins using metal-free PET-RAFT polymerizations under mild visible-light irradiation;(2017),ACS Macro Lett. 2017, 6, 4, 452–457 .

[9]. Sayed M. Derayea and Dalia M. Nagy:Application of a xanthenes dye, eosin Y, as spectroscopic probe in chemical and pharmaceutical analysis;(2018),Reviews in Analytical Chemistry 37(3) .

[10]. Ke Zhang,Zhengke Wang, Youliang Li, Zhiqiang Jiang, Qiaoling Hu,Minying Liu, Qingxiang Zhao. Dual stimuliresponsive N-phthaloylchitosan-graft-(poly(N-isopropylacrylamide)-blockpoly(acrylic acid) copolymer prepared via RAFT polymerization. (2013),Carbohydrate Polymers;Volume 92, Issue 1, Pages 662-667 .

[11]. Yasko Kodama, Murat Barsbay, Olgun Guven:Radiation-induced and RAFT-mediated grafting of poly(hydroxyethyl methacrylate) (PHEMA) from cellulose surfaces. (2014);Radiation Physics and Chemistry;Volume 94, Pages 98-104 .

[12]. Xueming Bao, Yuanyuan Yu,Qiang Wang, Ping Wang and Jiugang Yuan: 'Graft to' modification of lignin by the combination of enzyme-initiated reversible addition fragmentation chain transfer and grafting. (2019),ACS Sustainable Chem. Eng. 2019, 7, 15, 12973–12980 .

[13]. David Moore's world of fungi: where mycology starts. [n.d] .

[14]. Kogel-Knabner, W.Amelung: Dynamic chemistry and preservation of organic matter in soils.(2013); Elsevier,vol.12 (pp.157-215) .

[15]. Derong Lu, Congming Xiao,Fei Sun:Controlled grafting of poly(vinyl acetate) onto starch via RAFT polymerization.(2011); Journal of Applied Polymer ScienceVolume 124, Issue 4 p. 3450-3455.

[16]. Zhonghan Feng, Huining Wang, Maosheng Liu, Tao Chen,Yan Liu, Wenying Xu,Haiyan Wang, Jingquan Liu:In situ grafting of PEG Acrylate on drugs with aliphatic hydroxyl functionalities via RAFT polymerization to synthesize drug/polymer conjugates with improved water solubility.(2021),European Polymer Journal Volume 142, 110123 .

[17]. Bruce Cree:Demyelinating and inflammatory disorders of the central nervous system. [n.d]