Evaluation of Chitosan Derivatives for the Delivery of Salicylic Acid

P.SATHYAPRIYA

(15PCH012)

Thesis Submitted To

Avinashilingam Institute For Home Science And Higher Education For Women

Coimbatore-641 043

In Partial Fulfilment Of The Requirements For The Degree Of

Master Of Science In Chemistry

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S. Subramanian 10/4/17
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LIST OF ABBREVIATIONS AND ACRONYMS

CS	Chitosan
NMC	N-Maleyl Chitosan
NMC-g-PVA	N-Maleyl Chitosan grafted with poly vinyl alcohol
PVA	Poly Vinyl Alcohol
SA	Salicylic Acid
mg	Milligram
ug	microgram
EE	Entrapment Efficiency
YP	Yield Percentage
GP	Grafting Percentage
DMF	Dimethyl Formamide
DMSO	Dimethyl Sulphoxide
CAN	Ceric Ammonium Nitrate
TGA	Thermo Gravimetric Analysis
FTIR	Fourier Transform Infrared Spectroscopy

INTRODUCTION

INTRODUCTION

“The art of medicine consists of amusing the patient while nature cures the disease.”

- Voltaire

The medicine word is derived from the Latin word ' ars medicina', meaning 'the art of healing'. The medicine is a drug or herb used to maintain health or treat a health issue. The articles intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease in man or other animals; articles (other than food) intended to affect the structure or any function of the body of man or other animals are drugs.

The history of medicine, as practiced by trained professionals, shows how societies have changed in their approach to illness and disease from ancient times to the present. In the primitive civilizations, there existed no notion of symptoms and causes of diseases. An ailment was considered a supernatural and uncontrollable occurring, attributed to the forces of nature and those beyond it. Consequently, the cure of the ailment was also left as a task to nature itself. In rare cases, spontaneous natural interaction would result in a favourable change in health, however, most of the times, this did not happen. As a result, human life was short-lived. The present age is in utter contrast. Not only are most common diseases curable, there are well established norms of leading life in a certain manner so that these ailments do not trouble a human being. This tremendous achievement is a boon of medical science. No wonders medicine is considered the most essential branch of all sciences, as its impact on human beings is immediate and indispensible. Medicine is a specialization in health sciences, with the sole aim of preventing and alleviating the ill effects of a disease. Medicine is a vast study that applies its theories to ensure a healthy life for human beings through the use of tablets, drugs, syrups, etc.

Clinicians historically have attempted to direct their interventions to areas of the body at risk or affected by a disease. Depending on the medication, the way it is delivered, and how our bodies respond, side effects sometimes occur. These side effects can vary greatly from person to person in type and severity. For example, an oral drug for seasonal allergies may cause unwanted drowsiness or an upset stomach.

Administering drugs locally rather than systemically (affecting the whole body) is a common way to decrease side effects and drug toxicity while maximizing a treatment's impact. A topical (used on the skin) antibacterial ointment for a localized infection or a cortisone injection of a painful joint can avoid some of the systemic side effects of these medications. There are other ways to achieve targeted drug delivery, but some medications can only be given systemically.

Drug delivery technologies modify drug release profile, absorption, distribution and elimination for the benefit of improving product efficacy and safety, as well as patient convenience and compliance. Drug release is from: diffusion, degradation, swelling, and affinity-based mechanisms. Drug Delivery Technology is to provide new strategies for the delivery of biologically active compounds at the right dose, at the right time and at the right place. In order to achieve this, novel drug delivery systems are designed and the interactions of these delivery systems with biological systems are investigated at the (sub) cellular, tissue and organism level, both in vitro and in vivo. The goal of all sophisticated drug delivery systems, therefore, is to deploy medications intact to specifically targeted parts of the body through a medium that can control the therapy's administration by means of either a physiological or chemical trigger. To achieve this goal, researchers are turning to advances in the worlds of specific technology.

Current research on drug delivery systems can be described in four broad categories: routes of delivery, delivery vehicles, cargo, and targeting strategies.

Routes of Delivery

Medications can be taken in a variety of ways—by swallowing, by inhalation, by absorption through the skin, or by intravenous injection. Each method has advantages and disadvantages, and not all methods can be used for every medication. Improving current delivery methods or designing new ones can enhance the use of existing medications.

Delivery Vehicles

Biotechnology advances are leading to improved medications that can target diseases more effectively and precisely. Researchers have begun to reformulate drugs so they may be more safely used in specific conditions. The more targeted a drug is,

the lower its chance of triggering drug resistance, a cautionary concern surrounding the use of broad-spectrum antibiotics.

Cargo

Perhaps the most obvious route to improving disease treatment would be to focus on the medications themselves. In addition to drugs and novel vaccines, researchers are also exploring the use of genes, proteins, and stem cells as treatments.

Targeting Strategies

Working backwards is sometimes an effective way to solve a problem. In drug delivery research, this means starting with a delivery method. The target may be whole organs (heart, lung, brain), tissue types (muscle, nerve), disease-specific structures (tumor cells), or structures inside of cells.

The method by which a drug is delivered can have a significant effect on its efficacy. Some drugs have an optimum concentration range within which maximum benefit is derived, and concentrations above or below this range can be toxic or produce no therapeutic benefit at all [1]. On the other hand, the very slow progress in the efficacy of the treatment of severe diseases, has suggested a growing need for a multidisciplinary approach to the delivery of therapeutics to targets in tissues.

The advanced drug delivery systems have been focused on targeted drug delivery fields. The novel drug delivery is involved with the improvement of the capacity of drug loading in drug carriers, cellular uptake of drug carriers, and the sustained release of drugs within target cells The development of new and efficient drug delivery systems is of fundamental importance to improve the pharmacological profiles of many classes of therapeutic molecules. Many different types of drug delivery systems are currently available.

Beaded delivery formulations are the method used to achieve long-acting drug levels associated with the convenience of once-a-day dosing. The active drug is overlaid on the beads and encased in a delivery capsule. The drug delivery from this system is acid sensitive, in that drug levels are dependent on gastric acidity for release.

Possible systems for drug delivery-colloidal drug carriers: Colloidal drug carrier systems such as micellar solutions, vesicle and liquid crystal dispersions, as well as nanoparticle dispersions consisting of small particles show great promise as drug delivery systems. The goal is to obtain systems with optimized drug loading and release properties, long shelf-life and low toxicity. The incorporated drug participates in the microstructure of the system, and may even influence it due to molecular interactions, especially if the drug possesses amphiphilic and/or mesogenic properties.

Colon-specific drug delivery: Delivery of drugs into systemic circulation through colonic absorption represents a novel mode of introducing peptide and protein drug molecules and drugs that are poorly absorbed from the upper gastrointestinal (GI) tract. Oral colon-specific drug delivery systems offer obvious advantages over parenteral administration. Colon targeting is naturally of value for the topical treatment of diseases of the colon such as Crohn's disease, ulcerative colitis and colorectal cancer. Sustained colonic release of drugs can be useful in the treatment of nocturnal asthma, angina and arthritis. Peptides, proteins, oligonucleotides, and vaccines are the potential candidates of interest for colon-specific drug delivery. Sulfasalazine, ipsalazide, and olsalazine have been developed as colon-specific delivery systems for the treatment of inflammatory bowel disease.

Carbon Nanotube Drug Delivery: Nanomaterials, carbon nanotubes (CNT) have emerged as a new alternative and efficient tool for transporting and trans locating therapeutic molecules. CNT can be functionalised with bioactive peptides, proteins, nucleic acids and drugs, and used to deliver their cargos to cells and organs.

Use of polymeric micelles as pharmaceutical carriers. Micellization of biologically active substances is a general phenomenon that increases the bioavailability of lipophilic drugs and nutrients. Currently used low-molecular-weight pharmaceutical surfactants have low toxicity and high solubilisation power towards poorly soluble pharmaceuticals.

The success of trans dermal drug delivery has been severely limited by the inability of most drugs to enter the skin at therapeutically useful rates. Recently, the

use of micron-scale needles in increasing skin permeability has been proposed and shown to dramatically increase trans dermal delivery, especially for macromolecules.

In addition to the widespread application of polymers in manufacturing different materials, they are also used in several formulations and devices for drug delivery. When developing drug delivery systems, it is important to control how much of the drug is being released – too much of the drug at once can be harmful to the body, but too little of it may limit its effectiveness. Delivery of drugs at the optimal dosage for optimal lengths of time will make them more effective and more powerful.

It is with the use of polymers that manufacturers are able to deliver drugs more and more effectively. Some of the unique characteristics of polymers that make them versatile in drug delivery systems include:

- Wide molecular weight distributions
- Variety of visco-elastic properties
- Special characteristics associated with phase transitions
- Able to contract when heated
- Variety of dissolution times
- Specialized chemical reactivity
- Tolerate a variety of manufacturing methods

Application Scopes of Polymers in Drug Delivey System

Polymers are playing important role in pharmaceuticals. They are used as binders in tablet, increases solubility of poorly soluble drugs, used as film coatings on drugs to disguise their taste and enhances their stability etc. Some polymers which are used in drugs are discussed below.

Biodegradable Polymers

Biodegradable polymers have either hydrolytically or proteolytically labile bond in their backbone to make it chemically degradable. At present two types of biodegradable polymers exists: natural polymers and synthetic polymers. Collagen

and gelatin are two natural biodegradable polymers that are mostly used in drugs . Collagens are biocompatible, non-toxic, can be easily isolated and purified in large quantities. Gelatin is a thermoreversible polymer . Gelatin is easily available, have low antigen profile and have low binding affinity to drug molecules. All these properties make it suitable for drug delivery. Gelatin is cross-linked with glutaraldehyde to prepare it for drug delivery system. Synthetic biodegradable polymers are also present that include PLA, PLGA, PGA, poly(phosphazenes), poly(caprolactone), poly(anhydride), poly(phosphoesters), poly(cyanoacrylates), poly(acrylic acid), poly(amides), poly(ortho esters), polyethylene glycol, and polyvinyl alcohol and poly (isobutylcynoacrylate), poly(ethylene oxide), and poly(paradioxane). Among these, PLGA, the copolymer of PLA and PGA are mostly used polymers in drug delivery . Large numbers of biodegradable synthetic polymers rely on the hydrolytic cleavage of ester bonds.

Polyethylene glycol: Polyethylene glycol is a hydrophilic polymer. Some features like low toxicity, lack of immunogenicity, antigenicity and excellent biocompatibility make it preferred polymer. Its hydrophilic nature provides the protection to protein from any immune response.

Polyesters: They have esters bond in the main chain. Due to their biocompatible and biodegradable feature, PLA, PGA and their copolymer PLGA and poly (caprolactone) have been extensively used.

Polyanhydrides: Polyanhydrides are biocompatible and bioabsorbable materials. They can be easily removed from the body because they can be degraded into their diacid counter parts in vivo.

Polyamides: They contain the repeated unit of amide group and are hydrophilic in nature. Due to the presence of amide groups and hydrogen bonds, they have good mechanical properties and show high polar behaviour. They are used to deliver low molecular weight drugs.

Polyorthoesters: A number of studies have been done on the use of polyorthoesters as encapsulating material for various drugs.

Polyaprolctone: PCL have been taken into consideration to be used as implantable biomaterial because it has ester linkage that can be hydrolysed in physiological conditions. It can also be used for preparation of long term implantable devices because it degrades very slowly.

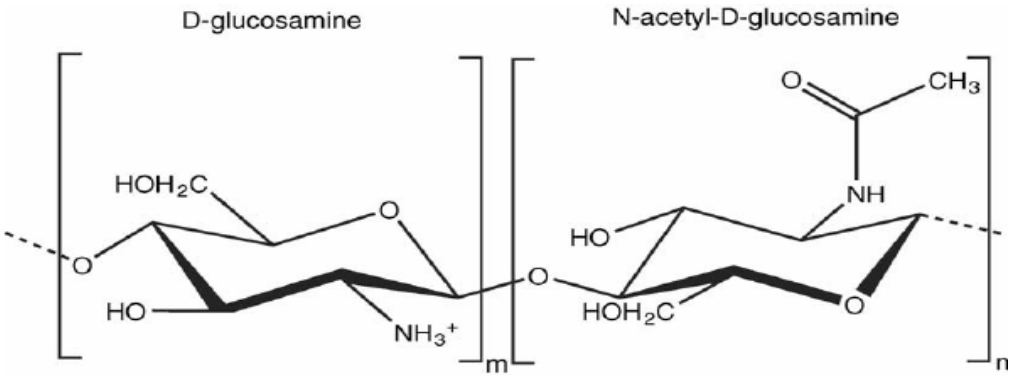
Smart Polymers: They are high performance polymers which change according to the environment they are residing in. Even a small change in the environment can bring large changes in the polymer's properties. They can change the conformation, adhesiveness and water retention properties in response to pH change. They are used for production of hydrogels and other materials. These properties of smart polymers make them suitable for utilization in drug formulations. Some smart polymer are formed by the cross linking of the pH sensitive smart polymeric chains. The polymer composition, the nature of the ionizable groups, the hydrophilicity of the polymer backbone and the cross linking density decide the behaviour of the smart polymers. The cross linking density affects the permeability of the solute inversely, the higher the cross linking density, the lower the permeability . Alginate gel beads are co-precipitated with a biologically active agent to form a sustained release gels. This gives the advantage of high loading of drugs while achieving better protein stability. LCST is a polymer, which have been tested in controlling drug delivery matrices. Copolymerisation of the NIP AAm with alkyl methacrylates maintains the temperature sensitivity because it increases its mechanical strength. There is reduction in the transportation of the bioactive molecules out of the polymers by surrounding the LCST with a thick layer of poly NIP AAm polymer.

Chitosan: A Promising Biopolymer in Drug Delivery Applications

Chitosan' the natural cationic polymer derived from chitin has received growing attention mainly due to their biodegradable, biocompatible, non-toxic, mucoadhesive and ability to target specific delivery properties. Chitosan has itself many medicinal properties like antimicrobial, antioxidant, low immunogenicity etc. which enhance its potential in different biomedical applications.

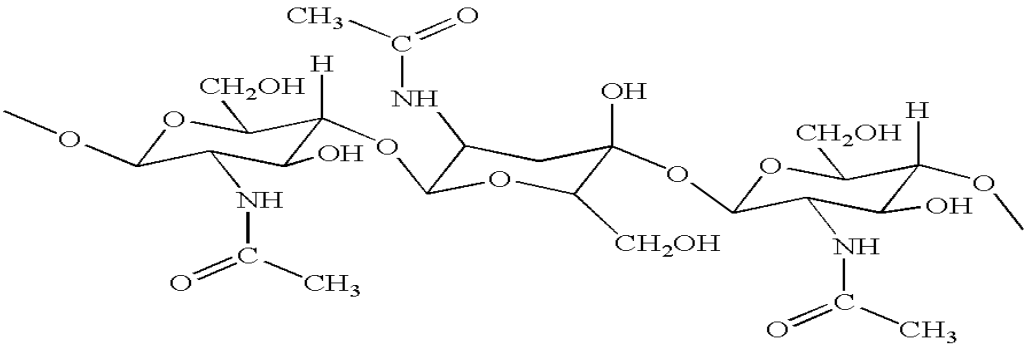
Chitosan is a cationic linear copolymer polysaccharide made up of random distribution of β (1→4) linked 2- amino- 2- deoxy- D- glucose (D-glucosamine) and

2- acetamido- 2- deoxy- D- glucose (N- acetyl- D- glucosamine) units. The structure is shown in **Figure (1)**



Fig(1) Molecular structure of Chitosan

and it is very similar to cellulose, in which the C-2 hydroxyl groups are replaced by acetamido residue. However owing to the presence of large percentage of nitrogen (6.89%), chitosan shows much commercial interest than synthetically substituted cellulose (1.2%). This provides chitosan chelating properties. Chitosan is typically obtained by extensive deacetylation of chitin, an abundant polysaccharide found in crustacean shells.



Fig(2) Molecular structure of Chitin

Chitosan offers outstanding biological properties due to which it has gained enormous importance in various applications in pharmaceutical and biomedical areas e.g. in drug delivery, tissue engineering, gene delivery etc. The primary amino groups in the polymer backbone of Chitosan provide positive charge on its surface. Due to its unique structure with poly cationic surface, along with capability of forming inter and intramolecular H- bonding, Chitosan has been regarded as a good candidate for the development of novel pharmaceutical products.

Chitosan in drug delivery

The remarkable physical, chemical and biological properties like easily modifiable and non toxicity make Chitosan a potential material in designing formulations for drug delivery in the gastrointestinal tract. The poly cationic nature of Chitosan makes it able to interact with the negatively charged mucous membrane and thereby increases the adhesion to the mucosa and as a result enhances the time of contact for penetration of drug molecules through it. It can act as permeation enhancer for hydrophilic drugs which have poor oral bioavailability due to interaction with cell membrane which may open the tight junctions in the membrane

Another important feature of using chitosan as drug carrier is its metabolic degradation in the body. Chitosan provides easy elimination process after drug administration, generally by renal clearance; however, this applies for Chitosan with suitable molecular weight. For very large molecular weight Chitosan, enzyme degradation is required. This rate of degradation depends on the molecular weight and degree of acetylation of the polymer. The possible site of degradation may be liver and kidney. Chitosan can be used as a diluents / filler in the drug delivery systems. It act as inactive ingredient added to tablet or capsule in order to control the release of drug.

The present invention relates generally to Chitosan polymer matrices for the controlled release of salicylic acid. More particularly, this invention describes methodology for preparing highly porous spherical polymer matrices.

OBJECTIVES

- The present study aimed to modify Chitosan to N-Maleyl Chitosan (NMC) and to graft it to poly vinyl alcohol (PVA).
- To confirm the modification through UV and FT-IR spectral data.
- To study the thermal stability of the new Chitosan drug carriers.
- To analyze the drug loading capacity and release behaviour of CS, NMC & NMC-PVA using SA as a model drug at various pH

REVIEW OF LITERATURE

REVIEW OF LITERATURE

Within the past 20 years, a considerable amount of work has been published on chitosan and its potential use in drug delivery systems. In contrast to all other polysaccharides having a monograph in a pharmacopeia, chitosan has a cationic character because of its primary amino groups. These primary amino groups are responsible for properties such as controlled drug release, mucoadhesion, in situ gellation, transfection, permeation enhancement, and efflux pump inhibitory properties. Due to chemical modifications, most of these properties can even be further improved. Within this review, an overview on the advantages of chitosan for various types of drug delivery systems is provided.

Selected studies on chitosan-based NanoProducts for drug delivery systems

A chitosan-hydrazone-mPEG (CH-Hz-mPEG) copolymer which is stable at extracellular pH and cleaves at slightly acidic intracellular pH was synthesized and characterized. Blank polymeric nanoparticles (B-PNPs) and prednisone-loaded polymeric nanoparticles (P-PNPs) were then formulated by dialy-sis/precipitation method. The cell-specific ligand, atrial natriuretic peptide (ANP) was then conjugated to P-PNPs (ANP-P-PNPs) by a coupling reaction. Particle size and morphological analyses revealed uni-form spherical shape of PNPs. In vitro pH dependent degradation of PNPs was investigated. Drug release profile of ANP-P-PNPs indicated a slow release of prednisone at pH 7.4, but a rapid release at pH 5.0due to the cleavage of hydrazone linkage. Cytotoxicity studies demonstrated greater compatibility of B-PNPs compared to ANP-P-PNPs. Cellular internalization of ANP-P-PNPs was higher than P-PNPs owing to receptor-mediated endocytosis. The results from this investigation support the hypothesis that chitosan based ANP-P-PNPs could act as an intracellular pH-responsive and targeted drug delivery system.**(Antoniraja etal.,2017)**

Nanoparticles of two Chitosan derivatives – N-succinyl-chitosan (SC) and N-glutaryl-Chitosan (GC) – were developed as passive transport systems for taxanes (paclitaxel and docetaxel) using an ionic gelationtechnique with sodium tripolyphosphate. These nanoparticles had an apparent hydrodynamic diameterof

300–350 nm, a _-potential of 25–31 mV, an encapsulation efficiency of 21–26%, and a drug loadingefficiency of 6–13%. DLS and SLS analysis shows that the nanoparticles have a unimodal size distributionand spherical form. Drug release kinetics of the taxane-loaded nanoparticles demonstrates that morethan 50% of the loaded taxane could be released upon the degradation of the nanoparticles after targeteddelivery. The drug-loaded SC and GC nanoparticles exhibit high cytotoxicity towards AGS cancer cell linesand their antitumor activity is consequently enhanced when compared with free taxanes.**(Skorika etal.,2017)**

Currently, targeted nano particles (NPs) are rapidly being developed to overcome various bottlenecks of antitumor agents, such as poor solubility in aqueous solution, poor pharmacokinetics, a lack of selectivity and undesirable side effects in healthy tissues. In recent years, chitosan, a cationic polysaccharide, has been widely explored for the targeted delivery of antitumor agents due to its unique physic chemical land biological properties, such as biocompatibility, biodegradability, mucoadhesive feature, absorption enhancement and active functional groups for chemical modifications. This article reviews the recent developments in various target-specific nanoparticles based on chitosan and its derivatives, includingpassive, active and stimuli-sensitive targeting strategies. In addition, the target mechanisms and the keyefficacy factors are illuminated**.(Zhanga etal.,2016)**

To develop a potential nano carrier for the topical ocular administration of curcumin (CUR), a novel thio-lated Chitosan was synthesized by the covalent binding between N-acetyl-l-cysteine (NAC) and Chitosan(CS) to surface modify the nano structured lipid carrier loaded CUR (CUR-NLC). And the superiorities of the CS-NAC co polymer coated CUR-NLC over Chitosan oligosaccharides (COS) or Carboxymethyl Chi-tosan (CMCS) modification were also verified in detail. As expected, the increment in particle size and the reversal of zeta potential occurred after surface decorating, and the most prominent electro positivity was obtained for the CS-NAC-CUR-NLC group. Additionally, the utilization of the CS-NAC coating demon-strated an effectively controlled release over 72 h and attained a 6.4 and 18.8 fold increase in apparent permeability coefficients (Papp) compared with the CUR-NLC and the self-made eye drops, respectively. Meanwhile, the clearance rate of the NLC labeled with Rhodamine B was significantly delayed in the pres-ence of CS-NAC. By contrast, CS-NAC-CUR-NLC was superior to the COS and CMCS coated

ones in view of in vitro release, drug permeability and corneal retention. Moreover, the results of the in-vivo and in-vitro characteristics demonstrated that the promoting effect of CMCS coating was relatively weaker than COS coated ones. Ocular irritation test was executed on the CS-NAC-CUR-NLC, neither a sign of toxicity nor irritation to the external ocular tissues was observed. In conclusion, CS-NAC-CUR-NLC possesses a greater potential as an ocular drug-delivery system comparing with the COS-CUR-NLC and CMCS-CUR-NLC**.(Lia etal.,2016)**

Zare-Akbari etal.,(2016) had prepared new pH-sensitive bionanocomposite beads based on car-boxymethyl cellulose (CMC) and ZnO nanoparticles for use as controlled release drug delivery systems.Fe3+ion as physical crosslinking agent was used to prepare ionic cross-linked bionanocomposite hydro-gel beads. Propranolol hydrochloride (PPN) has been chosen as a model drug. Characterization of the pH-sensitive bionanocomposite beads resulting from incorporation of different content of ZnO nanopar-ticles into CMC matric was carried out using different experimental techniques: XRD, FT-IR, TGA, SEMand EDX. Propranolol incorporation efficiency in beads was determined by UV–vis spectroscopy and was found to be high. Moreover, the swelling and drug release properties of the bionanocomposite hydrogels were investigated. The prepared bionanocomposite beads showed a pH sensitive swelling behavior with maximum water absorbing at pH 7.4. Also, it was found that the swelling ratio of ZnO/CMC hydrogels indifferent aqueous solutions was rather higher in comparison with its neat hydrogel. In vitro drug release test was carried out to prove the effectiveness of this novel type of bionanocomposite hydrogel beads as a controlled drug delivery system. A more sustained and controlled drug releases were observed for ZnONPs containing NaCMC beads, which increased by the increase in ZnONPs content.

Magnetite nanoparticles were synthesized by coprecipitation under ultrasonication followed by coating with chitosan. Polyvinyl alcohol (PVA) is then combined with the chitosan that coated the magnetitenanoparticles. The combination occurs by hydrogen binding and ionic cross-linking of the amino andhydroxyl groups of chitosan and PVA respectively. The magnetite nanoparticles have an average size of10.62 nm that was confirmed by TEM. The VSM measurements showed that nanoparticles were super-paramagnetic. The coatings on the core nanoparticles were estimated by AAS and the attachments ofcoating to the nanoparticles were confirmed

by FT-IR analysis. Physicochemical properties of nanopar-ticles were measured by DLS and zeta potential. Naked magnetite, chitosan and PVA coating have zetapotential of +36.4, +48.1 and −12.5 mV respectively. The unspecific adsorption and interaction betweennanoparticles and bovine serum albumin (BSA) were investigated systematically by UV–vis spectroscopymethod. The nanoparticles that were modified by PVA present low protein adsorption, which makes thema practical choice for preventing opsonization in clinical application and drug delivery**.(Shagholani.,2015)**

A new type of nanofibrous structure from chitosan bearing carboxymethyl-□-cyclodextrin (CS-*g*-□-CD) as a novel drug delivery system was synthesized by grafting carboxymethyl-□-cyclodextrin (CM □-CD) onto chitosan (CS) in the presence of water soluble 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) as the condensing agent and *N*-hydroxysuccinimide (NHS). Defect free mats containing CS-*g*-□-CD have been fabricated using electrospinning of an aqueous solution of poly(vinyl alcohol) (PVA)/CS-*g*-□-CD blends. The morphology and diameter of the electrospun nanofibers were examined by scanning electron microscopy (SEM). The average fiber diameter was in the range of 130−210 nm. SEM images showed that the morphology and diameter of the nanofibers were mainly affected by weight ratio of the blend at constant applied voltage. The results revealed that increasing CS-*g*-□-CD content in the blends decreases the average fiber diameter. It was observed that the PVA/CS-*g*-□-CD nanofibrous mat provided a slower release of the entrapped drug in compare to PVA/CS nanofibrous mat**.(Bazhban etal.,2013)**

Tamoxifen (Tam) has a broad spectrum of anticancer activity, but is limited in clinical application. **Viveka etal.,(2013)** explored the smart pH-responsive drug delivery system (DDS) based on Chitosan (CH) nanoparticles (NPs) for its potential in enabling more intelligent controlled release and enhancing chemotherapeutic efficiency of Tamoxifen. Tamoxifen was loaded onto CH-nanoparticles by forming complexes and Tamoxifen was released from the DDS much more rapidly at pH 4.0 and 6.0 than at pH 7.4, which is a desirable characteristic for tumor-targeted drug delivery. Tamoxifen-loaded CH nanoparticles induced remarkable improvement in anticancer activity, as demonstrated by MTT-assay, AO/EtBr and Hoechst nuclear staining. Furthermore, the possible signaling pathway was explored by RT-PCR. For instance, in human breast cancer MCF-7 cells, it was demonstrated that Tamoxifen-

loaded CH nanoparticles increase intracellular concentration of Tamoxifen and enhance its anticancer efficiency by inducing apoptosis in a caspase-dependent manner, indicating that drug loaded nanoparticles could act as an efficient DDS importing Tamoxifen into target cancer cells.

Chitosan (CS)–polylacticacid (PLA)–polyethylene glycol (PEG)–gelatin (G) nanoparticles, a novel drug vehicle for the controlled release of an antitubercluosis drug, rifampicin (RIF) was developed and its chemical and biochemical activities were studied by various standard methods. The designed carriers CS,PEG and G nanoparticles were prepared by emulsion solvent evaporation technique, and then used for entrapping RIF. Linking was confirmed by FTIR spectroscopy. The surface morphology of the nanoparticles was studied using scanning electron microscope and polarizing microscope. The influence of process variables, on particle size, zeta potential and matrix entrapment of RIF was studied. The encapsulation and loading capacity were evaluated, and an in vitro release of RIF was assessed using the dialysis method. The effect of nanoencapsulation of RIF on the antibacterial activity of RIF against Mycobacterium strains was evaluated. The preliminary results clearly suggested that the cross linked CS–PLA–PEG–G matrix may be a potential polymeric carrier for controlled delivery of RIF**.(Rajan etal.,2013)**

An attempt has been made to encapsulate anti-tuberculosis drug, Rifampicin (RIF) with a model drug delivery system. The designed carrier Chitosan (CS) and polyethylene glycol 600 (PEG) nanoparticles were prepared by Ionic gelation technology, and then used for entrapping RIF. The PEG binding with CS-RIF changed the character and the surface of the nanoparticles and slightly increased its particle size, while the drug encapsulation was also increased. PEG bind with CS-RIF achieved a significantly prolonged retention compared with non-coated CS-RIF. Various parameters and methodologies such as loading capacity, encapsulation efficiency, SEM, FTIR and in vitro release have been utilized for characterization of nanoparticles. The release of drugs was influenced by their initial drug concentration, indicating that the release of drugs could be controlled by varying the initial drug concentration. All results suggested that CS and CS-PEG nanoparticles are promising system for delivering RIF in treatment of tuberculosis. **(RAJAN etal.,2012)**

Reza etal.,(2010) has designed a new extended release gastroretentive multiparticulate delivery system by incorporation of the hydrogel beads made of

chitosan. As the first part of a continued research on conversion of N-sulfonato-N,carboxymethylchitosan (NOCCS) to useful biopolymer-based materials, large numbers of carboxylic functional groups were introduced onto NOCCS by grafting with polymethacrylic acid (PMAA). The free radical graft copolymerization was carried out at 70 ◦C, bisacrylamide as a cross-linking agent and persulfate as an initiator. The equilibrium swelling studies were carried out in enzyme-free simulated gastric and intestinal fluids (SGF and SIF, respectively). Also, the satranidazole as a model drug was entrapped in nano-gels and in vitro release profiles were established separately in both enzyme-free SGF and SIF. The drug release was found to be faster in SIF. The drugrelease profiles indicate that the drug release depends on their degree of swelling and cross-linking.

Many peptide and protein derived therapeutics cannot be administered through oral rout because of the proteolytic condition of gastro-intestinal tract and their low bio-availability. Insulin is a peptide drug which is widely used in diabetics as repeated daily injection. Due to the fact that there are receptors for dipeptides and vitamine B12 in small intestine, novel derivatives of chitosan and trimethyl Chitosan conjugated with glycyl-glycine, alanyl-alaninie and vitamine B12 were synthesized and characterized. The structure of conjugates as well as substitution of different functional groups was confirmed by different instrumental analytical methods such as Fourier transform infrared, magnetic resonance, and X-ray diffraction spectroscopy. Nano-particles of aforementioned loaded with insulin were prepared and their size, surface electrical charge and morphology characterized and their release profile were studied. The results are promising and reveal that these new chitosan and trimethyl Chitosan derivatives are potential vehicles for protein and peptide drug molecules**.(Jafary etal.,2011)**

pH responsive chitosan based drug delivery systems

(Reza etal.,(2015) has reported the synthesis of magnetic and pH-sensitive beads derived from_carrageenan and carboxymethyl Chitosan for drug delivery. The magnetic Fe3O4nanoparticles were synthesized inside amixture of biopolymers by in situ method. The structural properties of hydrogel beads were characterized by TEM, SEM, XRD, and VSM techniques. The swelling ratio of beads indicated pH-dependent proper-ties with maximum water absorbing at pH 7.4. Introducing

magnetic nanoparticles caused a decrease in swelling capacity from 16.4 to 10 g/g. Drug loading and release efficiency were investigated using diclofenac sodium as a model system. The in vitro drug release studies exhibited significant behaviours on the subject of physiological simulated pHs and external alternative magnetic fields. The maximum cumulative release was around 82% at pH 7.4. The presence of magnetite nanoparticles certainly influenced the drug release patterns. The response of beads to external stimulus makes them as good candidates for novel drug delivery systems.

Carboxymethyl chitosan was prepared, characterized, and then photo-induced graft copolymerized with poly(ethylene glycol) under a nitrogen atmosphere in aqueous solution using 2,2-dimethoxy-2-phenyl acetophenone (DMPA) as the photo-initiator by **ElSherbiny etal.,(2010)**. The grafting copolymerization process was confirmed and the resulting copolymers were characterized using differential scanning calorimetry (DSC), FTIR spectroscopy, 2D-X ray diffraction, and elemental analysis. The kinetics of the grafting reactions was also studied. Under the applied experimental conditions, the optimum grafting values were obtained at:CMCs = 0.2 g, PEGA = 249 mM, DMPA = 10.4 mM at a 2 h reaction time. Some of the resulting copolymers were selected and used in the presence of methylene bisacrylamide (MBA) as a crosslinking agent to develop pH-responsive hydrogel matrices. The swelling characteristics and the in vitro release profiles of 5-fluorouracil (5-FU), as a model drug, from the hydrogels were investigated. The results revealed that the hydrogel matrices developed in this study can be customized to act as good candidates in drug delivery systems.

The new polyelectrolyte complex gel beads based on phosphorylated chitosan (PCS) were developed for controlled release of ibuprofen in oral administration. The PCS gel beads were readily prepared from soluble phosphorylated chitosan by using an ionotropic gelation with counter polyanion, tripolyphosphate (TPP), at pH 4.0. The beads were characterized by scanning electron microscopy (SEM) for morphological studies. The in vitro drug release behavior in various pH media was studied using ibuprofen as a model drug. Ibuprofen was highly loaded, around ,90%, in the PCS gel beads. The release percents of ibuprofen from PCS gel beads were found to be increased as the pH of dissolution medium increased. The release rate of ibuprofen at pH 7.4 was noticeably higher than the release rate at pH 1.4 due to the ionization of

phosphate groups and high solubility of ibuprofen at pH 7.4. These factors suggest that the PCS gel beads may be useful for controlled drug delivery system through oral administration by avoiding the drug release in the highly acidic gastric fluid region of the stomach**.(Phyu etal.,2003)**

Development of novel pH sensitive interpenetrating polymeric network (IPN) beads composed of chitosan-glycine-glutamic acid cross linked with glutaraldehyde and their use for controlled drug release was discussed by **Rani etal.(,2010).** A comparative study has been carried out on these IPN beads with the beads that of chitosan, chitosan-glycine and chitosan-glutamic acid cross linked with glutaraldehyde. The beads were characterized by FTIR to confirm the cross linking reaction and drug interaction with cross linked polymer in beads, scanning electron microscopy (SEM) to understand the surface morphology and internal structure and DSC to find out the thermal stability of beads. The swelling behavior of the beads at different time intervals was monitored in solutions of pH 2.0 and pH 7.4. The release experiments were performed in solutions of pH 2.0 and pH 7.4 at 37°C using chlorpheniramine maleate (CPM) as a model drug. The swelling behavior and release of drug were observed to be dependent on pH, degree of cross linking and their composition. The results indicate that the newly constructed cross linked IPN beads of chitosan-glycine-glutamic acid might be useful as a vehicle for controlled release of drug. The kinetics of drug release from beads was best fitted by Higuchi's model in which release rate is largely governed by rate of diffusion through the matrix.

Polymer grafted drug delivery systems of Chitosan

Bashir etal.,(2016) had prepared unique biodegradable, biocompatible, swellable, and pH responsive N-succinyl chitosan-g- Poly (methacrylic acid) hydrogels through free radical mechanism for oral administration of theophylline. In this method, ammonium persulfate (APS) and N, N0-methylenebisacrylamide (MBA) were used as initiator and crosslinking agent, respectively. The physical properties characterization was performed by Fourier transform infrared (FTIR) spectroscopy, X-ray diffraction (XRD), differential scanning calorimetry (DSC), field emission scanning electron microscope (FESEM), and rheometer. The results clearly confirmed the successful formation of N-succinyl chitosan-g- Poly (methacrylic acid) gel. In

vitro degradation of hydrogels was found dependent on the ratio of monomers to crosslinking concentration. The effect of concentration of monomers, initiator, and crosslinking agent, pH and ionic strength of salts on swelling behavior was investigated. The results revealed the strong influence of these parameters, on swelling properties. Hydrogel prepared with high concentration of initiator and low crosslinking agent showed maximum swelling. The swelling showed good fitting to second order rate equation and the swelling kinetics data demonstrated the swelling behavior followed non-Fickian anomalous transport mechanism. Furthermore, theophylline loading and encapsulation efficiency (EE %) were found to be 14.5e23.5% and 58e94%, respectively. However, the in vitro release profile of theophylline was found dependent on pH, concentration of monomers, initiator, and crosslinking agent. The maximum release was found to be 90% in simulated intestinal fluid (SIF). The drug release data showed good fitting to Ritger-Peppas model. Moreover, the chemical activity of theophylline was also investigated and found that the drug maintained its chemical activity after in vitro release.

The grafting of poly(ethylene glycol) functionalized by ester groups (MeO-PEG-ester) onto Chitosan was studied and optimized using different reaction conditions. In a first procedure, the grafting was made from 6-O-triphenylmethyl-chitosan after protection of primary hydroxyl groups and in a second one, it was made directly onto Chitosan. NMR spectroscopy was an important tool to study these reactions and the grafting is unequivocally showed up. Moreover, for each procedure, the solubility and surface properties of the obtained copolymers were evaluated and compared.**(Lebouca etal.,2015)**

The graft copolymerization of methyl acrylate (MA) onto Chitosan in aqueous medium was investigated using potassium persulfate (KPS) as initiator. The grafting conditions were optimized by studying the effects of the polymerization variables (the initiator concentration, the ratio of monomer to chitosan, and reaction temperature) on the percentage of grafting (PG). PG was found to depend on these variables, and the highest grafting percentage (256 %) could be obtained at Chitosan = 1 g, KPS = 4.5 9 10-3 M, methyl acrylate monomer = 6 g, T = 60 _C and t = 180 min. The graft copolymer was characterized by Fourier transform infrared spectra analysis, thermogravimetry (differential thermogravimetry, differential scanning calorimetric), X-ray powder diffraction as well as CP-MAS 13C NMR spectroscopy. These analyses are highly confirmed the formation of poly(methyl acrylate) grafted chitosan

(PMAGC). Furthermore, the gelation of the grafted polymers (PG 68,122, 218 and 256 %) in distilled water has been studied, and the results revealed that the percentage of swelling number increase with increasing PGof the polymers. Controlled release of niacin (vitamin B3) from the hydrogel of the grafted polymers (PG 68, 122 and 256 %) in aqueous medium has been studied using ultraviolet absorption to follow quantities released at different times (for each experiment: PMAGC 100 mg, niacin 2.46 mg, distilled water 100 ml). The study was repeated again with same conditions except the using of 4.92 mg of niacin instead of 2.46 mg (PG of the grafted polymer is256 %). The diffusion coefficient (D, cm2/h) of niacin from the hydrogel of the grafted polymer (PG 256 %) was calculated depending on Higuchi model (diffusion coefficient of the first load is 0.00194 cm2/h while 0.00255 cm2/h of the second load).**(Al-Karawi.,2014)**

Chitosan-graft-poly (2-hydroxyethyl methacrylate-co-itaconic acid) has been synthesized for different feed ratios of 2-hydroxyethyl methacrylate and itaconic acid and characterized by FTIR, thermogravimetry and swelling in simulated biological fluids (SBF) and evaluated as a drug carrier with model drug, tramadol hydrochloride (TRM). Grafting decreased the thermal stability of Chitosan. FT-IR spectra of tablet did not reveal any molecular level (i.e. at <10 nm scale) drug–polymer interaction. But differential scanning calorimetric studies indicated a probable drug–polymer interaction at a scale >100 nm level. The observed Korsmeyer–Peppas's power law exponents (0.19–1.21) for the in vitro release profiles of TRM in SBF and other drugs such as 5-fluorouracil (FU), paracetamol (PCM) and vanlafaxine hydrochloride (VNF) with the copolymer carriers revealed an anomalous drug release mechanism. The decreased release rates for the grafted Chitosan and the enhanced release rate for the grafts with increasing itaconic acid content in the feed were more likely attributed to the enhanced drug–matrix matrix interaction and polymer–SBF interactions,**(Gounder etal.,2012)**

Biodegradable graft copolymer, Chitosan -graft-poly(ε-caprolactone) (CS-g-PCL) was synthesized viaring opening polymerization and characterized by 1H NMR and FTIR spectroscopy. Then graft copolymers were self-assembled into micelles as drug delivery system. To evaluate drug-polymer compatibility, the Flory Hugginsinteractionparameterbetween5-fluorouraci(5-Fu)andhydrophobicsegmentwas calculated. The result was in agreement with experimental data from drug loading content and drug loading efficiency. Meanwhile, DLS and TEM were utilized to

evaluate the trend of particle size and morphology in aqueous solution with different repeating units of ε-CL. The in vitro drug release data was fitted with three kinetic models, usually applied in the drug delivery system. Results indicated that the release of 5-Fu was control lable and there lease half-time could reach has long as 54.46h, much slower than that offree5 Fu. Cyto oxicity evaluation and cellular apoptosis study suggested good biocompatibility of CS-PCL micelles.Moreover,5-Fuloaded micelles could delay the release of drug and exert comparable cytotoxicity against A549cells**.(Guaetal.,2014)**

Chitosan(CS)–polylacticacid (PLA)–polyethylene glycol (PEG)–gelatin (G) nanoparticles, a novel drug vehicle for the controlled release of an antitubercluosis drug, rifampicin (RIF) was developed and its chemical and biochemical activities were studied by various standard methods. The designed carriers CS, PEG and G nanoparticles were prepared by emulsion solvent evaporation technique, and then used for entrapping RIF. Linking was confirmed by FTIR spectroscopy. The surface morphology of the nanoparticles was studied using scanning electron microscope and polarizing microscope. The influence of process variables, on particle size, zeta potential and matrix entrapment of RIF was studied. The encapsulation and loading capacity were evaluated, and an in vitro release of RIF was assessed using the dialysis method. The effect of nano encapsulation of RIF on the antibacterial activity of RIF against Mycobacterium strains was evaluated. The preliminary results clearly suggested that the cross linked CS–PLA–PEG–G matrix may be a potential polymeric carrier for controlled delivery of RIF.**(Rajan etal.,2013)**

Carboxymethyl chitosan was prepared, characterized, and then photo-induced graft copolymerized with poly(ethylene glycol) under a nitrogen atmosphere in aqueous solution using 2,2-dimethoxy-2-phenyl acetophenone (DMPA) as the photo-initiator by **(ElSherbiny etal.,2010)** The grafting copolymerization process was confirmed and the resulting copolymers were characterized using differential scanning calorimetry (DSC), FTIR spectroscopy, 2D-X ray diffraction, and elemental analysis. The kinetics of the grafting reactions was also studied. Under the applied experimental conditions, the optimum grafting values were obtained at: CMCs = 0.2 g, PEGA = 249 mM, DMPA = 10.4 mM at a 2 h reaction time. Some of the resulting copolymers were selected and used in the presence of methylene bisacrylamide (MBA) as a crosslinking agent to develop pH-responsive hydrogel matrices. The

swelling characteristics and the in vitro release profiles of 5-fluorouracil (5-FU), as a model drug, from the hydrogels were investigated. The results revealed that the hydrogel matrices developed in this study can be customized to act as good candidates in drug delivery systems.

Three model drugs (insulin, diclofenac sodium, and salicylic acid) with different pI or pKa were used to prepare drug-Chitosan micro/nanoparticles by ionic interaction. Physicochemical properties and entrapment efficiencies were determined. The amount of drug entrapped in the formulation influences zeta potential and surface charge of the micro/nanoparticles. A high entrapment efficiency of the micro/nanoparticles could be obtained by careful control of formulation pH. The maximum entrapment efficiency did not occur in the highest ionization range of the model drugs. The high burst release of drugs from Chitosan micro/nanoparticles was observed regardless of the pH of dissolution media. It can be concluded that the ionic interaction between drug and Chitosan is low and too weak to control the drug release**.(Boonsongrit etal.,2006)**

A chitosan-hydrazone-mPEG (CH-Hz-mPEG) copolymer which is stable at extracellular pH and cleaves at slightly acidic intracellular pH was synthesized and characterized. Blank polymeric nanoparticles(B-PNPs) and prednisone-loaded polymeric nanoparticles (P-PNPs) were then formulated by dialy-sis/precipitation method. The cell-specific ligand, atrial natriuretic peptide (ANP) was then conjugated to P-PNPs (ANP-P-PNPs) by a coupling reaction. Particle size and morphological analyses revealed uni-form spherical shape of PNPs. In vitro pH dependent degradation of PNPs was investigated. Drug release profile of ANP-P-PNPs indicated a slow release of prednisone at pH 7.4, but a rapid release at pH 5.0due to the cleavage of hydrazone linkage. Cytotoxicity studies demonstrated greater compatibility of B-PNPs compared to ANP-P-PNPs. Cellular internalization of ANP-P-PNPs was higher than P-PNPs owing to receptor-mediated endocytosis. The results from this investigation support the hypothesis that chitosan based ANP-P-PNPs could act as an intracellular pH-responsive and targeted drug delivery system**.(Antoniraja etal.,2017)**

Polymer Matrix Used For Salicylic Acid Release

Salicylic acid is a common active ingredient used in topical formulation for therapeutic treatment such as acne due to its keratolytic property . However, it may cause a mild to strong skin irritation to certain patients The reduction of antiacne agent irritancy through incorporation in the sustained release formulations such as liposome, microemulsion, hydrogel, and SLN has been reported. Hence, encapsulation of salicylic acid in the prolonged release delivery system could be a potential approach to minimize its side effects and reduce the application frequency, thus offering better patient compliance. The research works pertaining to the release systems used for Salicyclic acid are summarized below.

Salicylic acid was intercalated into an inorganic host consisting of ZnAl/MgAl_layered double hydroxides lamella by reconstruction method. Powder X_ray diffractograms showed that the basal spacing of the layered double hydroxide bearing salicylate as the intergallery anion expanded from 7.6 and 7.8 Å in the precursors to 14.49 Å and 14.85 in ZnAl and MgAl layered double hydroxide, respectively. These values suggest that the organic molecules form bilayers in the interlayer space. Fourier transform infrared study further confirmed intercalation of salicylate into the interlayer's of the layered double hydroxides. The thermal stability of the intercalated salicylic acid is significantly enhanced compared with the pure form before intercalation. Using the XRD results combined with a molecular simulation model, a possible representation of the salicylate anion positioning between the lamellar layers has been proposed. The in vitro drug release from intercalated material was remarkably lower than that from the corresponding physical mixture at pH 7.5. The kinetic analysis showed the importance of the diffusion through the particle in controlling the drug release rate. The obtained results show that hydrotalcite may be used to prepare modified release formulations**.(Haraketi etal.,2016)**

Blends between polythiophene (PTh) and a carrageenan hydrogel were fabricated as the matrix for the electric field assisted drug release. The pristine carrageenan and the blend films were prepared by thesolution casting using acetylsalicylic acid (ASA) as the anionic model drug and Mg2+, Ca2+, and Ba2+asthe crosslinking agents. The ASA was released by the Fickian diffusion

mechanism. The diffusion coef-ficient decreased with increasing crosslinking ratio or decreasing crosslinking ionic radii. The diffusion coefficients were greater with the applied electrical potentials by an order of magnitude relative to thosewithout electric field. Moreover, the diffusion coefficients with PTh as the drug carrier were higher than those without PTh. Thus, the presence of the conductive polymer in the hydrogel blend coupled with applied electric field is shown here to drastically enhance the drug delivery rate**.(Pairatwachapun etal.,2016)**

(Aguzzi etal.,2013) investigated desorption of 5-aminosalicilyc acid (5-ASA) adsorbed onto halloysite (HL). Desorption isotherms were fitted according to kinetic laws obtained considering release of 5-ASA from HL as the phase of desorption of the previously adsorbed drug molecules both inside the nanotubes of HL as onto the surface of clay particles and/or in the inter-particle spaces of their aggregates . Desorption isotherms has been also fitted with other equations frequently used in drug release kinetics studies. The best fitting corresponded to the kinetic model proposed; in agreement with the results of adsorption.

Hydroxypropyl methyl cellulose grafted with polyacrylamide (HPMC-g-PAM) hydro-gel was evaluated in vitro as a potential carrier for controlled release of 5-amino salicylic acid (5-ASA) by **(Das etal.,2013)**. The graft copolymer was developed by grafting PAM chains onto HPMC backbone using potassium per-sulphate as initiator. The swelling behaviour of hydrogel based tablet was investigated as a function ofpH and time in various buffer solutions similar to that of gastric and intestinal fluids. The % equilibrium swelling was found to be higher in case of simulated intestinal fluid (pH = 7.4) and lower in simulated gas-tric fluid (pH = 1.2), making an ideal matrix as required for colon specific drug delivery. The drug release study was performed at various pH values akin to the condition of GI tract. The release kinetics of 5-ASA showed non-Fickian diffusion behaviour. This indicates that the release is controlled by a combination of polymer relaxation or erosion of the matrix and diffusion of the drug from the swollen matrix.

Biofilm-associated infections are a major complication of implanted and indwelling medical devices like urological and venous catheters. They commonly persist even in the presence of an oral or intravenous antibiotic regimen, often resulting in chronic illness **(Nowatzki etal.,2012)** developed a new approach to inhibiting biofilm growth on synthetic materials through controlled release of salicylic

acid from a polymeric coating. Herein we report the synthesis and testing of a ultraviolet-cured polyurethane acrylate polymer composed, in part, of salicyl acrylate, which hydrolyzes upon exposure to aqueous conditions, releasing salicylic acid while leaving the polymer backbone intact. The salicylic acid release rate was tuned by adjusting the polymer composition. Anti-biofilm performance of the coatings was assessed under several biofilm forming conditions using a novel combination of the MBEC Assay™ biofilm multi-peg growth system and bioluminescence monitoring for live cell quantification. Films of the salicylic acid-releasing polymers were found to inhibit biofilm formation, as shown by bioluminescent and GFP reporter strains of Pseudomonas aeruginosa and Escherichia coli. Urinary catheters coated on their inner lumens with the salicylic acid-releasing polymer significantly reduced biofilm formation by E. coli for up to 5 days under conditions that simulated physiological urine flow.

Nanostructure polypyrrole (PPy) films templated with salicylate (SA), as a model drug, have been uti-lized as conducting molecularly imprinted polymer (CMIP) for potential-controlled selective loading andrelease. Two key parameters (applied potential and temperature) affecting on release kinetic were stud-ied using fluorescence spectrometry. The measured fluorescence intensity was related to the amountof SA released from the film. The film templated with SA exhibited good selectivity over some interfer-ence for loading. The PPy film as recognative absorbent has been applied for the selective loading andrelease of SA to the receptor solution. Characterization of the CMIP/SA using field emission scanningelectron microscopy (FE-SEM) has confirmed the nanostructured morphology of the films. Kinetics ofsalicylate release from the CMIP was investigated at various applied potentials and temperatures. TheAvrami's equation was used to analyze release kinetics. This equation showed good fit for SA releaseprofiles. Kinetics analysis based on Avrami's equation showed that the release of SA was controlled andaccelerated by increasing potential and temperature. For potential treatments, the release parameter (n)represented a diffusive mechanism at open circuit condition and a first-order mode at applying elec-trochemical potentials. However, at open circuit condition, a diffusive mechanism was found almost inall temperature experiments. Release rate constants increased as a function of increasing temperature.Activation energy parameters (Ea, _G/=, _H/=and _S/=) and half-life time (t1/2) of drug release are alsoanalyzed as a function of applied potential. The relationship between the applied

potentials and acti-vation parameters was investigated and was shown that Eaand _G/=decreased linearly by increasingnegative applied potential.**(Shamaeli etal.,2013)**

The formulation of salicylate-based poly(anhydride-ester) (PAE) microspheres was optimized by altering polymer concentration and homogenization speed to improve the overall morphology. The microspheres were prepared using three salicylate-based PAEs with different chemical compositions comprised of either a hetero atomic, linear aliphatic, or branched aliphatic moiety. These PAEs broadened the range of complete salicylic acid release to now include days, weeks, and months. The molecular weight (Mw), polydispersity index (PDI) and glass transition temperature (Tg) of the formulated polymers were compared to the unformulated polymers. In general, the Mw and PDI exhibited decreased and increased values, respectively, after formulation, whereas the Tg changes did not follow a specific trend. Microsphere size and morphology were determined using scanning electron microscopy. These microspheres exhibited smooth surfaces, no aggregation, and size distributions ranging from 2 to 34 lm in diameter. In vitro release studies of the chemically incorporated salicylic acid displayed widely tunable release profiles**.(Rosario-Mele´ndez etal.,2013)**

Psyllium, a medicinally active natural polysaccharide, has been modified with polyacrylamide to develop the hydrogels; those can act as the potential candidate for novel drug delivery systems. In the present studies, the release dynamics of model drugs (salicylic acid and tetracycline hydrochloride) from the drug-loaded hydrogels have been discussed, for the evaluation of the drug release mechanism and diffusion coefficients. It has been observed that diffusion exponent ‘n’ have 0.68 and 0.74 values and gel characteristic constant ‘k’ have 1.625 · 10_2 and 1.272 · 10_2 values, respectively, for the release of salicylic acid and tetracycline hydrochloride in distilled water from the drug loaded hydrogels. Therefore, drug release from the drug loaded hydrogels through Non-Fickian or Anomalous diffusion mechanism where the rate of drug diffusion and rate of polymer relaxation were comparable. The effect of pH on the release pattern of tetracycline has been studied by varying the pH of the release medium. However, in each release medium, the Initial diffusion coefficient was observed to be more than the late time diffusion coefficient**.(Singh etal.,2007)**

a fully automated system for the in vitro release testing of semisolid dosage forms based on SIA technique was described by **(Klimundov etal.,2005).**The system

was tested for monitoring release profiles of different ointments containing 3% of salicylic acid (Belosalic, Diprosalic, Triamcinolone S). The native fluorescence of salicylic acid was used for fluorimetric detection. Phosphate buffer pH 7.4 was the receptor medium; samples were taken at 10 min intervals during 6 h of the release test; and each test was followed by calibration with five standard solutions. The linear calibration range was 0.05–10 _gml-1 (r = 0.9996, six standards); the maximal SIA sample throughput for this system was 120 h-1, sample volume being 50 _l and flow rate 50 _l s-1. The detection limit for salicylic acid was 0.01 _gml-1.

Poly(D,L-Lactide) of high molecular weight Mv. was prepared by ring-opening bulk polymerization of D,L-Lactide and characterized in terms of Mv , melting point and swelling behavior in buffer solution. Samples of the polymers with low and high Mv (2000 and 22000 respectively) loaded with various amounts of salicylic acid (SA) were immersed in a buffer solution and the release of SA was recorded. The results obtained showed that swelling of the poly(D,L-Lactide) samples obeyed Fick's law, especially for those with high molecular weight, where biodegradation proceeds slowly. The release of SA seemed to follow a simpli®ed relationship which is linear with time, at least for the early stages of delivery. The extent of linearity is dependent on the content of the acidic SA, which probably accelerates decomposition of the high molecular weight products**.(Andreopoulos etal.,2001)**

An overview of the literature on salicylic acid release systems and chitosan derivatives as drug carrier point out that water soluble pH responsive chitosan derivative may be apt for sustainable release of salicylic acid. Consequently efforts have been made to prepare water soluble pH responsive chitosan derivatives and tested as drug carrier for salicylic acid carrier systems.

MATERIALS AND METHODS

MATERIALS AND METHODS

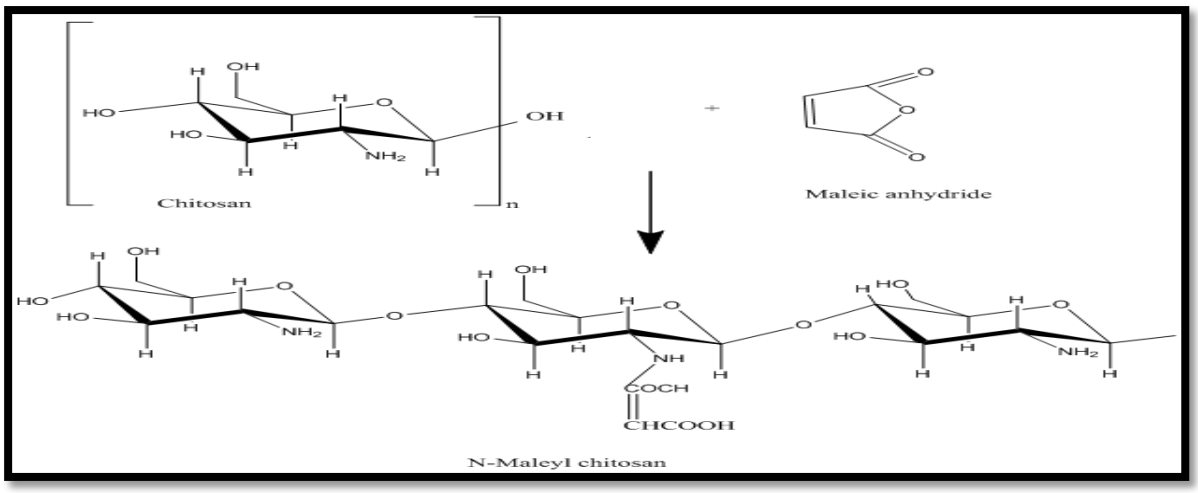
Chitosan was modified with maleic anhydride and further it was grafted with Poly vinyl alcohol. Chitosan and its derivatives were used to study the release behaviour of Salicylic acid in different pH with time.

Materials

Chitosan with 75% of degree of deacetylation, Poly vinyl alcohol (molecular weight 1, 40,000) and Maleic anhydride were supplied by HiMedia. Salicylic acid (Merck) LR grade Glacial acetic acid, Acetone, Citric acid, Ceric Ammonium Nitrate (CAN), Ethanol, Disodium Hydrogen Phosphate, Dimethyl Sulphoxide (DMSO) and Dimethyl Formamide (DMF) were used for the synthesis. Magnetic stirrer (Spinot model MC 01) was used for the preparation of polymers. pHmeter (DeLure pH meter -107) was used to carry out the drug release study.

Method of Preparation

Preparation of N-Maleyl Chitosan : Two gram of Chitosan was dissolved in 200ml of 1% acetic acid at room temperature. The solution was allowed to stand for half an hour at room temperature with constant stirring. Maleic anhydride (2.4g) of was dissolved in 5ml of ethanol solution. The maleic anhydride solution was added drop wise to the Chitosan solution with constant stirring. The mixture was allowed to stand for 15 hours at room temperature with constant stirring. The product was precipitated and washed with acetone to remove the unreacted compounds. The product was air dried. A schematic representation of the preparation is mentioned below.



Figure(3) : Schematic representation for the preparation of N-Maleyl Chitosan

Grafting with poly vinyl alcohol (NMC-g-PVA)

Graft polymerization of Poly Vinyl Alcohol on to the N-Maleyl Chitosan was carried out using free radical polymerization method. The prepared N-Maleyl Chitosan was grafted on PVA without precipitating. A required quantity of initiator Ceric Ammonium Nitrate (CAN) was added to the N-Maleyl Chitosan solution to generate the free radical sites in the polymer chain. Then 500mg of poly vinyl alcohol in 5ml of hot water was added to the mixture with continuous stirring at room temperature .The reaction was carried out for 6 hours .The product was kept overnight and then precipitated using acetone. The product was washed with acetone several times to remove the un reacted compounds. The product was air dried.

The Percentage of Yield & Grafting

Percentage of yield and grafting was calculated using the formulae:

$$\text{Percentage Yield} = \frac{\text{Weight (g) of the graft polymer}}{\text{Weight (g) of PVA + Weight (g) of Polymer}} \quad (1)$$

$$\text{Percentage Grafting} = \frac{\text{Weight (g) of the graft polymer}}{\text{Weight (g) of PVA}} \quad (2)$$

Characterization

Chitosan and its derivatives were characterised using UV spectrophotometer (AU-2701UV–VIS Double beam spectrophotometer), The FTIR spectra (FT/IR-4600typeA) , and thermal analysis studies were recorded using SII TG/DTA6300 Thermal analyser.

UV-Vis spectroscopy

AU-2701UV–VIS Double beam spectrophotometer was used to record UV spectrum. Absorption of UV-visible radiation results in a transition from a lower energetic level to a higher level occurring energy absorption from the atom equalto the energy difference between both levels. This energy difference lies between 125 and 650kj/mole in most of the molecules. The energy order of various orbitals is as

$$\sigma < \pi < n < \pi^* < \sigma^*$$

When a polymer is subjected to some modifications on change, by having the UV-visible spectra of the base material and the synthesized sample, the changes can be analyzed if any one of the material achieve a UV-Vis range. Synthesized graft polymer (NMC-g-PVA) achieved a particular range. So absorption behaviour was measured by UV-visible absorption spectra (Systronics-PC based double beam spectrometer 2202). The absorption was recorded in the range of 200-800nm.

Fourier transform infrared spectroscopy (FTIR)

Infrared spectroscopy (FT/IR-4600typeA) is an important technique in analytical chemistry. It is an easy way to identify the presence of certain functional groups in a molecule. Also, one can use the unique collection of absorption bands to confirm the identity of a pure compound or to detect the presence of specific impurities. The FT-IR spectral data for pure and SA loaded polymer matrices were collected from FTIR (FT/IR-4600typeA) within the range (400-4000 cm^{-1}).

Thermogravimetric Analysis (TGA)

Thermo gravimetric analysis (a record of change of the mass with time or temperature) is extremely helpful, for example: When testing polymers like plastics, rubbers, composites laminate adhesives or coatings. It is inherently quantitative, and therefore an extremely powerful thermal technique, but gives no direct chemical information. The main information obtained from TGA is the thermal stability of the polymers.

Related materials can be compared at elevated temperature under the required atmosphere. The TG-Curve can help to clarify decompositions. The thermal behaviour of the modified N-Maleyl Chitosan and synthesized graft polymer (NMC-g-PVA) was analysed using Thermogravimetric analyser (Exstar-SII-TG/DTA 6300) in the temperature range 50-550^{o}C at nitrogen atmosphere.

Solubility Test:

Solubility of the prepared N-Maleyl Chitosan and the graft polymer (NMC-g-PVA) was tested in common solvents like water and ethanol. The ability of Dimethyl Sulphoxide (DMSO) and Dimethyl Formamide (DMF) to dissolve the polymers was also tested at room temperature.

Preparation of Calibration Curve

In this procedure the absorbance of a number of standard solutions of the reference substance at various concentrations (0.1,0.2,0.3,0.4,0.5,0.6, 0.7,0.8,0.9,1.0) were prepared and measured on Double beam spectrophotometer and calibration graph was constructed .The concentration of the drug in solution was read from the graph as the concentration corresponding to the absorbance of the solution. The calibration graphs of salicylic acid were made to determine the amount of drug release from the drug loaded polymeric matrix in different buffersolutions (distilled water, pH = 3, 4, 5 and 6 buffer).

Drug Loading to the Polymer Matrix

The loading of a drug onto polymer solutions carried out by directly mixing the drug with the polymer solution, precipitated out with acetone and dried.1g of Chitosan was dissolved in 100ml of 1% acetic acid. The mixture was allowed to stand for half an hour at room temperature with constant stirring. Salicylic acid (10mg) was added to the solution and kept for 15 hours at room temperature and then precipitated using acetone. The product was air dried.

Preparation of salicylic acid loaded N-Maleyl Chitosan

1g of N-Maleyl Chitosan is dissolved in 100ml of water. The mixture was allowed to stand for half an hour at room temperature with constant stirring. Salicylic acid (10mg) was added to the solution and kept for 15 hours at room temperature and then precipitated using acetone. The product was air dried.

Preparation of salicylic acid loaded N-Maleyl Chitosan graft poly vinyl alcohol

1g of N-Maleyl Chitosan graft poly vinyl alcohol was dissolved in 100ml of water. The solution was allowed to stand for half an hour at room temperature with constant stirring .Salicylic acid (10mg) was then added to the solution ,kept for 15 hours at room temperature and then precipitated using acetone. The product was air dried.

Evaluation of Drug Entrapment Efficiency

Entrapment Efficiency (EE):

$$\frac{\text{Total amount of drug loading (mg)} - \text{Free drug in supernatant (mg)}}{\text{Total amount of drug loading (mg)}}$$

Drug release from the polymer matrix

In vitro release studies of the drug were carried out by placing dried and loaded sample (50mg) in definite volume of releasing medium (50ml) at room temperature. The amount of salicylic acid released was measured spectrophotometrically. The release studies for salicylic acid were done in distilled water, pH=3, 4, 5 and 6 buffers. The drug release was measured after fixed interval of time (5min) and release dynamics of drug was studied.

Preparation of Buffer Solution

Buffer solution was prepared by using 0.1M citric acid and 0.2 Disodium hydrogen phosphate mixed in various compositions according to the buffer 3,4,5 and 6.The 0.1M citric acid was prepared by dissolving 9.15g of citric acid in distilled water to make the volume 100ml with distilled water. The 0.2M Disodium Hydrogen Phosphate was prepared by dissolving 90.85g of Disodium Hydrogen Phosphate in distilled water to make the volume 100ml with distilled water.

Buffer solution of pH 3 was prepared by taking 79.45ml of0.1M citric acid and 20.55ml of 0.2M Disodium hydrogen phosphate and mixed together then checked by pH meter.

Buffer solution of pH 4 was prepared by taking 61.45ml of 0.1M citric acid and 38.55ml of 0.2M Disodium hydrogen phosphate and mixed together then checked by pH meter.

Buffer solution of pH 5 was prepared by taking 48.5ml of 0.1M citric acid and 51.5ml of 0.2M Disodium hydrogen phosphate and mixed together then checked by pH meter.

Buffer solution of pH 6 was prepared by taking 36.85ml of 0.1M citric acid and 63.15ml of 0.2M Disodium hydrogen phosphate and mixed together then checked by pH meter.

RESULT AND DISCUSSION

RESULT AND DISCUSSION

Efforts have been taken to conduct a study on " Evaluation of Chitosan Derivatives for the Delivery of Salicylic Acid". A brief summary of the literature showed that good drug delivery system should possess :

- It should be non toxic and bio combatable and physio chemical stable in vitro and in vivo
- Controllable and predicted rate of release
- Drug release does not affect the drug action
- Therapeutic amount of drug release
- Carrier should be bio degradable
- The preparation of delivery system should be easy

The present study has been conducted to explore the drug loading and releasing capacity of chitosan and its derivatives for salicylic acid.

The results pertaining to the present investigation are tabulated and discussed in the light of the objectives set forth under the following headings.

1. YIELD PERCENTAGE AND GRAFT PERCENTAGE
2. CHARACTERIZATION OF PREPARED POLYMERS:
    - 2.1 UV-Visible spectroscopy:
    - 2.2 FT-IR Spectroscopy
    - 2.3 Thermogravimetric analysis
    - 2.4 Solubility of Chitosan Derviative
3. DRUG LOADING AND RELEASING
    - 3.1 Calibration Curve
    - 3.3 Entrapment Efficiency
    - 3.3 Drug Release from the Polymer Matrix
    - 3.4 Effect of pH and Time on release behaviour SA from CS
    - 3.4 Effect of pH and Time on release behaviour SA from NMC
    - 3.5 Effect of pH and Time on release behaviour SA from NMC-g-PVA
    - 3.7 Assessment of Drug Releasing Capacity of Chitosan and its derivatives:
    - 3.8 Mechanism of Drug Loading and Releasing

1. Yield Percentage and Graft Percentage

Yield percentage indirectly indicates the loss of original compound during the process. In this preliminary study the yield percentage was very low namely 41.8%and 36.2% for N-Maleyl Chitosan and NMC-g-PVA grafting respectively. Efforts will be taken in the future study to improve the same.

The grafting percentage (GP) indicates the increasing weight of original Chitosan subjected to grafting with a monomer is calculated generally by the equation (1) & (2).

The GP values given above apparent or crude values and they do not indicate the true values, Since they are calculated for the mixture consisting of true graft co-polymer and the non grafted Chitosan. In the present study the GP value is 72.4% which indicates an effective grafting. The calculated values of YP and GP are shown in Table (1).

Samples	**Yield percentage(%Y)**	**Graft percentage(%G)**
N-Maleyl Chitosan(NMC)	41.8	-
Graft Polymer (NMC –g-PVA)	36.2	72.4

Table (1): Yield percentage and Graft percentage of NMC and NMC-g-PVA

2. CHARACTERIZATION OF PREPARED POLYMERS:

2.1 **UV-Visible spectroscopy**:

The UV-Vis spectra of CS, NMC, Graft polymer (NMC-**g**-PVA**)** are displayed in Figure. Chitosan is transparent in the UV-Vis region but NMC represents three absorption maxima at λmax=219,228, and 251nm.The λmax at 219,228nm corresponds to a π-π* transition of the conjugated π electrons of maleic anhydride while the absorption maxima at 251nm corresponds to n- π* and π-π* transitions indicates the incorporation of maleic anhydride into Chitosan backbone.

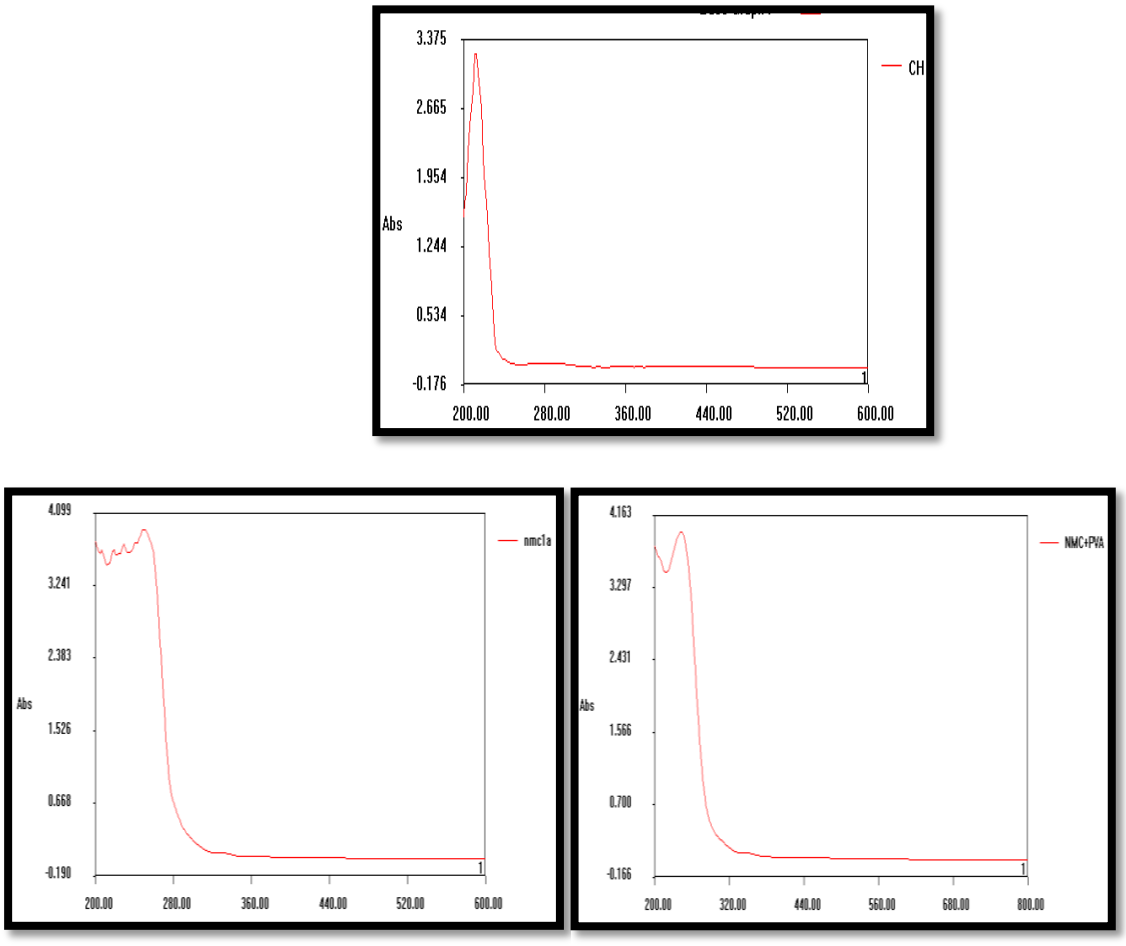


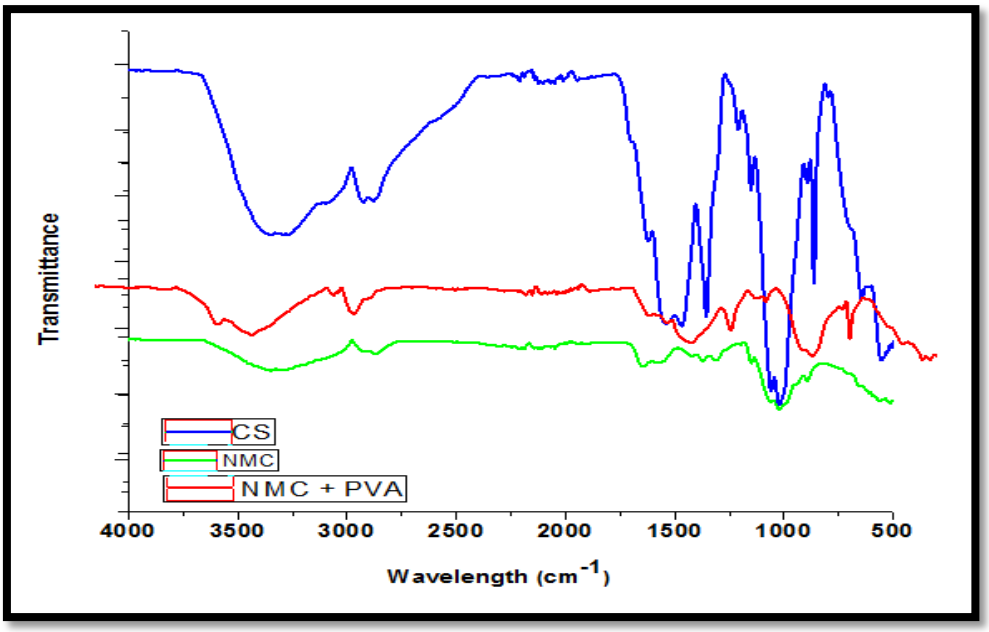
Figure 4: UV spectrum of a) Chitosan b) N-Maleyl Chitosan c) Graft polymer (NMC-g-PVA)

The UV-Vis spectrum of graft polymer (NMC-g-PVA) shows absorption maxima in the region 243nm. This corresponds to the n- π*transition of the polymer chain. The absence of absorption region π-π*transition confirms the grafting of PVA onto the Chitosan matrix

2.2 FT-IR Spectroscopy

The FT-IR spectra of CS, NMC & NMC-g-PVA are shown in fig.(5). The characteristic absorption peaks of Chitosan have been observed in 3367 cm^{-1} which is due to the OH stretching. The band at 1539 cm^{-1} is assigned for the NH bending (amide II) (NH_2) while the small peak at 1620 cm^{-1} is attributed to the C=O stretching. The bands at 2926, 1467, 1355 and 1209 are assigned to CH_2 bending due to pyranose ring. The characteristic peaks at 1058 cm-1 and 1020 cm-1 are due to stretching of C-O bond in glycosidic linkages of Chitosan.

The FT-IR spectrum of NMC shows the characteristic absorption peaks NH_2 and OH at 3305 cm^{-1} and 2870 cm^{-1} respectively; the absorption peak at 1645 cm^{-1} corresponds to stretching vibration of C=C; 1579 cm^{-1} shows the presence of NH bending and Secondary hydroxyl group absorption at1373 cm^{-1}. The characteristic peak at 1024 cm-1 due to stretching of C-O bond in glycosidic linkages of Chitosan. The decrease in intensity of amino group absorption confirms the utilization of NH2 group for the reaction with Maleic anhydride.



Figure(5) FT-IR of Chitosan and its Derivatives

The absorption peak at 3489 cm^{-1} and 3352 cm^{-1} represents the NH_2 & OH groups in NMC-g-PVA. The increase in intensity of these peaks is due to the incorporation of OH group from the grafted PVA. The band at 2926 cm^{-1} is assigned to CH_2 bending in pyranose ring. While the band at 1642 cm^{-1} represents the presence of C=C and the absorption at 1519 cm^{-1} is attributed to asymmetrical stretching of C-N bond in amide group. The characteristic peak at 1020 cm^{-1} due to stretching of C-O bond in glycosidic linkages of Chitosan.

The FT-IR spectra of CS, NMC & NMC-g-PVA after loading SA are shown in fig(6) . The broad band's present around 3300-2900 cm-1 is attributed to NH2 and OH stretching vibrations as well as inter and extra molecular hydrogen bonding in Chitosan molecules. The characteristic peak at 1633 and 1621 cm-1 appeared due to the amide linkage formed between SA and CS, NMC & NMC-g-PVA respectively.The absorption peaks around 760 to 680 cm^{-1} appeared in all the loaded matrices are assigned to be skeletal -CH vibrations of benzene ring. Thus the spectral data of loaded carrier confirmed the incorporation of SA into the polymer matrix.

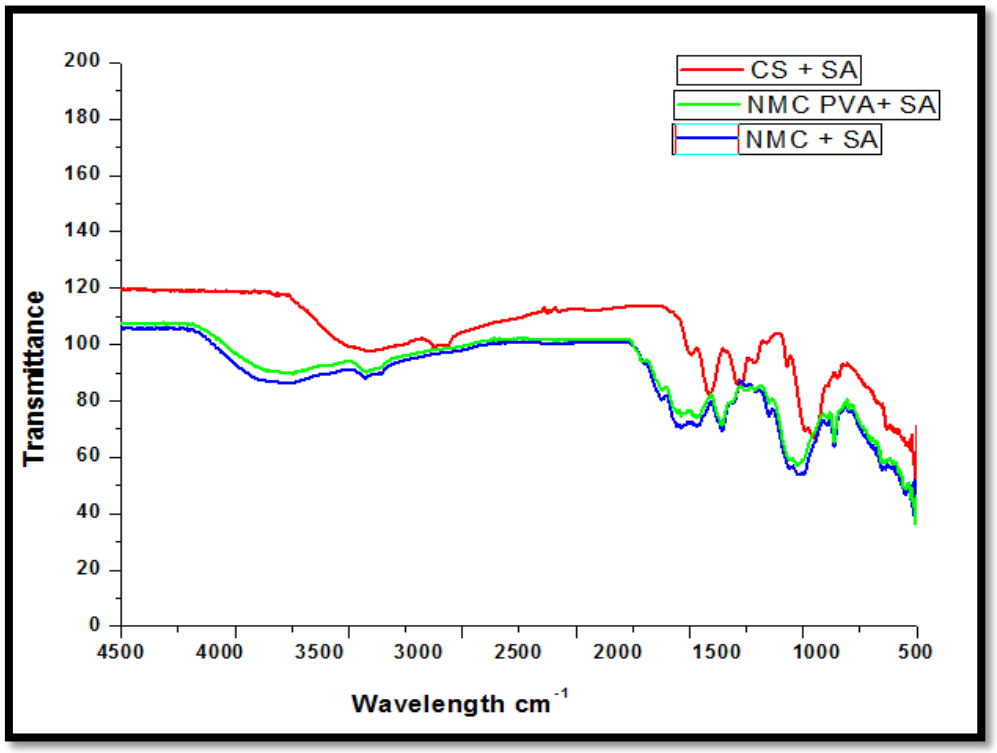


Fig (6) FT-IR of Chitosan and its Derivatives with SA

2.3 THERMOGRAVIMETRIC ANALYSIS

Chitosan thermogram showed two main decomposition stages with the first occurring in the range of 40-100°C attributed to the evaporation of water with the weight loss of 10%. The second decomposition stage occurred in the range of around 280-300°C due to the thermal degradation with the weight loss of about 60%.

The TGA thermograms of N-Maleyl Chitosan and grafted polymer (NMC-g-PVA) are shown in Figure 2. It can be found that the Chitosan derivative N-Maleyl Chitosan has undergone two step degradation. The first stage is at 40-190^{o}C with a weight loss of about 13% which is due to the vaporization of water and elimination of unstable fragments. At 190^{O}C the primary degradation starts, which may be due to the decomposition of anchored alkyl derivative and thereafter the breakdown of Chitosan main chains takes place.

The thermogram of grafted polymer (NMC-g-PVA) showed three stage degradation, at 40-180^{O}C, 230-310^{O}C and above 310 ^{O}C .The first one is due to the moisture and vaporization, The second stage occurs in 230-310^{O}C corresponding to the degradation of some volatile products in the polymer and also corresponds to the initial degradation of polyene residues which on further heating yield carbon and hydrocarbons. This thermal degradation step of the graft polymer confirms the successful grafting of PVA on to the N-Maleyl Chitosan matrix. Furthermore, the increase of maximal decomposition temperature (Tmax) for graft polymer is also attributed to the grafting of PVA with N-Maleyl Chitosan.

The thermal degradation study indicates that NMC is less stable than CS, and NMC-PVA is more stable than CS.

Polymer	**N-Maleyl Chitosan**	**Graft polymer (NMC-g-PVA).**
T_{max}(^{O}C)	338.3	345.5

Table(2) The data of thermogravimetric analysis of N-Maleyl Chitosan and Graft Polymer (NMC-g-PVA)

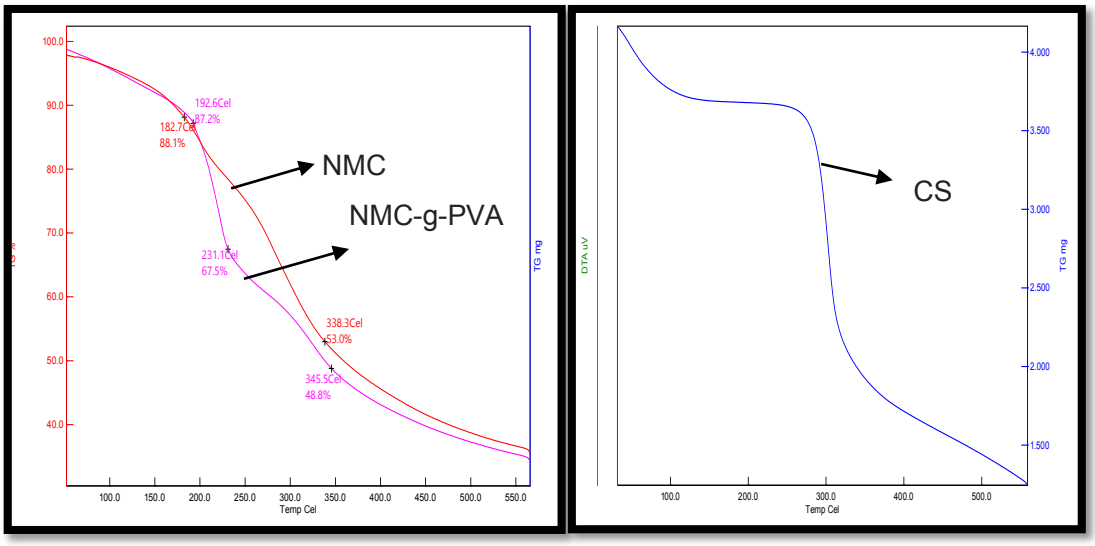


Figure (7): Thermographs of CS, NMC and NMC-g-PVA

2.4 Solubility of Chitosan Derviative NMC and NMC-g-PVA

The solubility of N-Maleyl Chitosan and the grafted polymer (NMC-g-PVA) was tested in protic solvent viz water and ethanol and organic solvent Dimethyl Sulphoxide (DMSO) and Dimethyl Formamide (DMF) the results are presented in both the products table are readily soluble in water.

Solvents	N-Maleyl Chitosan			NMC- g- PVA		
	Soluble	Partially soluble	Insoluble	Soluble	Partially Soluble	Insoluble
Water	✓			✓		
Ethanol			✓			✓
Dimethyl sulphoxide		✓			✓	
Dimethyl formamide		✓			✓	

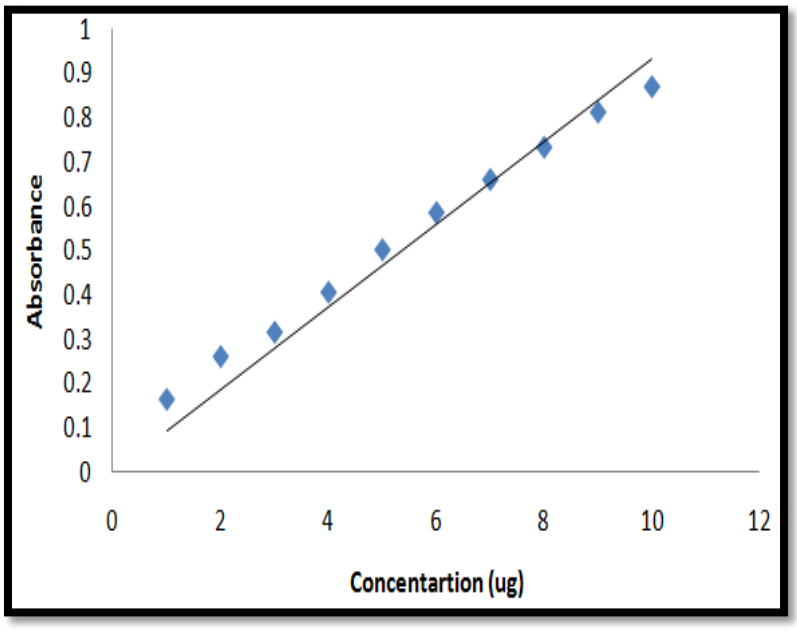
Table 3: Solubility Behaviour of prepared NMC and NMC-g-PVA

The water solubility is because of the decrease of hydrophobic amino group in NMC. The solubility of NMC-g-PVA is due to the increase in hydrophilic groups in PVA. The insolubility in ethanol may be due to the low dielectric constant of ethanol compared to water. The derivative and grafted polymer remain as macro molecules in ethanol. In spite of low dielectric constant, the partial solubility in DMSO is may be due to the bond formed between oxygen of Sulphoxide group and the carbonyl group present in NMC nd NMC-g-PVA. The tendency of DMF to form epoxide like structure with OH groups may cause for the partial solubility of Chitosan derivative and graft polymer.

3. DRUG LOADING AND RELEASING

3.1 Calibration Curve:

A calibration curve, also known as a standard curve, is a general method for determining the concentration of a substance in an unknown sample by comparing the unknown to a set of standard samples of known concentration. The intensity of UV absorbance at the wavelength region 200-240nm of standard salicylic acid solutions were determined and a calibration curve is shown in fig. (8).



Figure(8) Calibration Curve of Salicylic acid

The intensity of absorbance and the concentration are directly related. The intensity increased with increase in concentration of salicylic acid. 0.1655 & 0.8722 intensity of absorbance were noticed with 1 & 10 ug of salicylic acid respectively.

3.2 Entrapment Efficiency:

Entrapment efficiency describes the fraction of drug incorporated into polymer matrix compared to the total amount of drug that was added during study 200-240nm. The drug entrapped in the polymer matrices was calculated using UV spectrophotometer data which are given in the table (4)

Polymer	**% of EE**	**Time (h)**
CS	88	15
NMC	96	15
NMC+PVA	86	15

Table (4): Entrapment efficiency of polymer matrices

The entrapment efficiency of NMC is higher than the Chitosan, NMC showed 96% of EE. However after grafting with PVA, there is no significant increase in the entrapment of the drug. Introduction of maleyl group enhanced the drug holding capacity of the Chitosan matrix. The grafting of PVA does not affect the efficiency of entrapment. The order of entrapment efficiency is: **NMC>CS>NMC-PVA** 96% EE of NMC indicated the porous nature and the presence of active functional groups to hold the drug molecules.

3.3 Drug Release from the Polymer Matrix

The unique nature of hydrogels is the dependence of their properties on the pH of the medium. Environmental pH values have a large effect on the behaviour of the hydrogels. The three studied polymers being hydrogels their drug releasing capacity were studied at various pH ranging from 3-7. The influence of pH values of the buffer solutions on the release behaviour of the hydrogels at room temperature is shown in fig (9), (10), (11).

The release of water soluble drugs entrapped in a hydrogels occur only after water penetrates the polymeric networks through swell and dissolve the drug followed by diffusion along the aqueous path ways to the surface of the device. Therefore it is time dependent.

3.4 Effect of pH and Time on release behaviour SA from CS

From the fig.(9) of CS it was observed a gradual decrease in drug release from pH 3-5 and then a sharp transition from pH 5-7. This is because the pKa value of SA present in the polymer is about 2.97 and the carboxylic groups tend to dissociate at a pH less than 5. In the pH range of 5-7 the SA remains un-dissociated which is shown as the increase in concentration of SA in the medium.

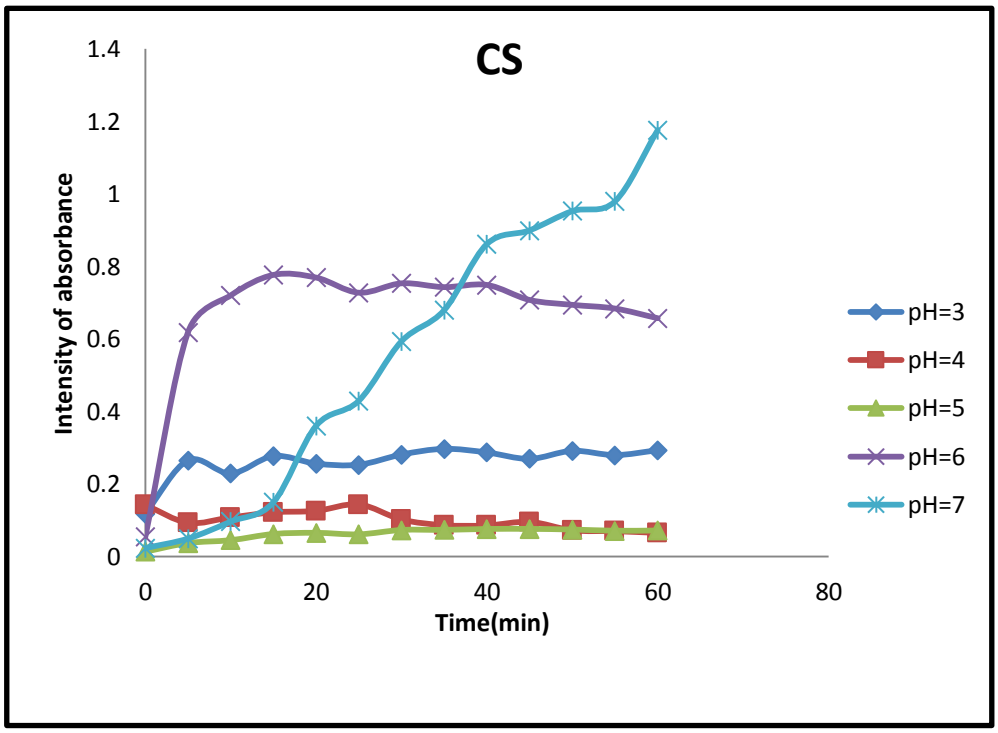


Figure (9) :Influence of pH on the SA release of Chitosan

The release behaviour of CS with time is given in Table (5). It was obviously observed that there is a gradual increase in release behaviour from pH 3-7 with time. The release of SA reached an equilibrium state after 40mins at all pH, indicating a sustainable releasing nature of the CS matix.

Time (min)	Weight of SA in (ug)				
	pH=3	pH=4	pH=5	pH=6	pH=7
0	0.1195	0.1427	0.0139	0.0546	0.0238
5	0.2656	0.0937	0.0377	0.6188	0.05
10	0.2293	0.1083	0.0457	0.7205	0.0968
15	0.2776	0.1225	0.0627	0.7772	0.15
20	0.2568	0.1264	0.0659	0.7698	0.361
25	0.2537	0.1443	0.0618	0.7281	0.43
30	0.2818	0.1026	0.0738	0.7539	0.5941
35	0.2975	0.087	0.0741	0.7435	0.68
40	0.2876	0.0862	0.0766	0.7495	0.8623
45	0.2699	0.0962	0.0768	0.7081	0.9
50	0.292	0.0729	0.075	0.6946	0.9531
55	0.2803	0.0704	0.0717	0.6844	0.98
60	0.2937	0.0657	0.0723	0.6577	1.1765

Table (5): Effect of pH on the release of SA from CS at different time intervals

3.5 Effect of pH and Time on release behaviour SA from NMC:

The sensitivity of drug release from NMC to the pH of the medium is depicted in the table (6) above. Effective release of SA was noticed at pH 6, compared to the other pH studied. Generally the release was better in the range of pH 4-6. SA is used in skin ointments to cure scaly patches, corns, calluses, and warts on the hands or feet. Since the average pH of human skin false between 4-6, the NMC would be a better carrier for SA compared to CS atthe targeted pH.

N-Maleyl derivative of Chitosan being selected as a targeted drug delivery system for SA, the effect of time on the release was established in the table (6). The rate of release of SA was increased upto 30mins and remained stable till 60mins. This period of the release is suitable to get adsorbed on the skin slowly and steadily.

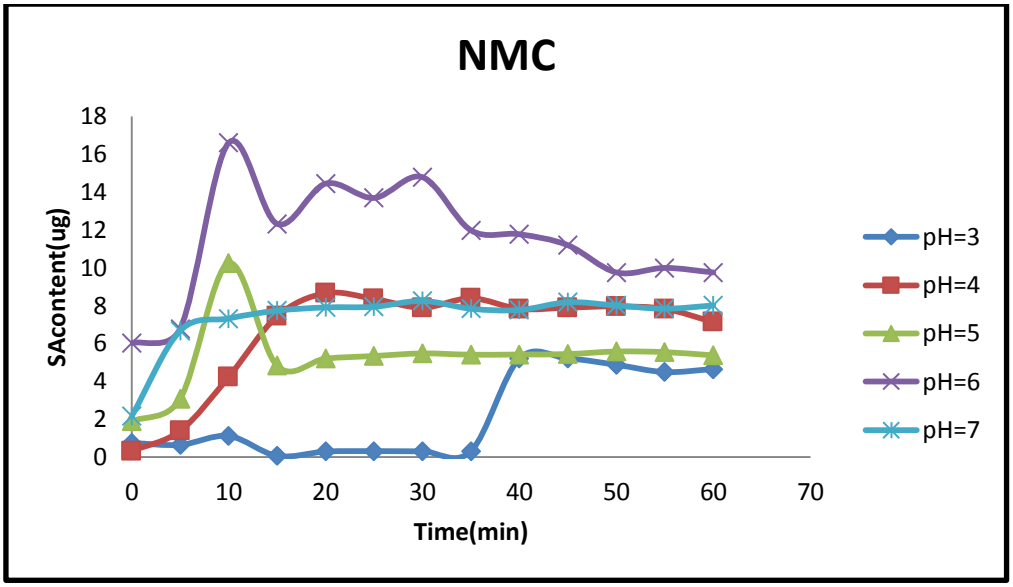
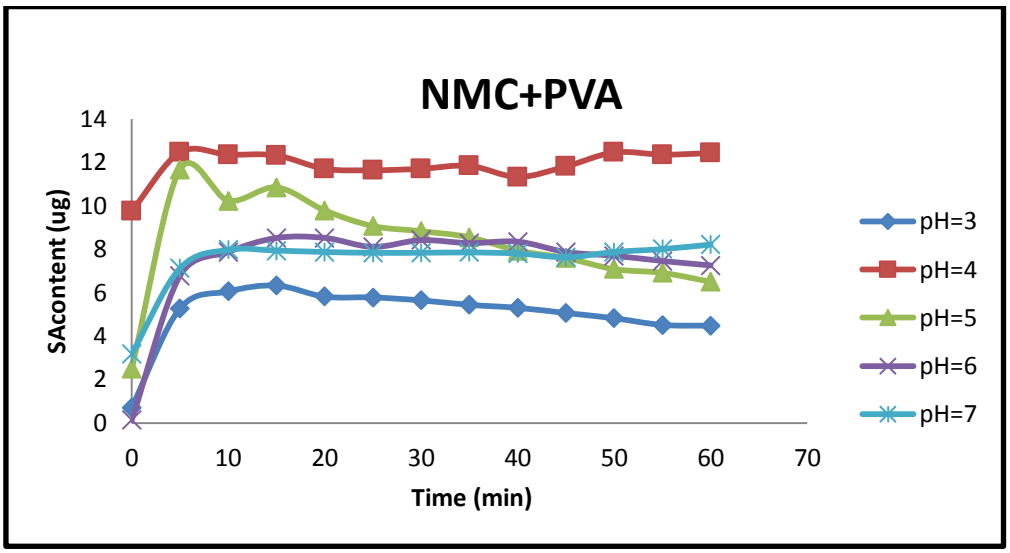


Fig (10) Influence of pH on the SA release of NMC

Time(min)	Weight of SA (ug)				
	pH=3	pH=4	pH=5	pH=6	pH=7
0	0.738	0.3079	1.8725	6.0175	2.1462
5	0.6378	1.3783	3.0718	6.7694	6.667
10	1.1046	4.2206	10.229	16.596	7.3166
15	0.0537	7.427	4.8182	12.3158	7.7283
20	0.281	8.6489	5.1942	14.4406	7.8996
25	0.3054	8.3508	5.3322	13.6863	7.9329
30	0.2932	7.888	5.4678	14.7832	8.2422
35	0.3054	8.385	5.4012	11.9755	7.8306
40	5.2006	7.8229	5.4113	11.7685	7.7616
45	5.2034	7.8889	5.4345	11.1879	8.1732
50	4.8682	7.9548	5.5701	9.7484	8.0019
55	4.484	7.822	5.5368	9.9887	7.8306
60	4.6409	7.1288	5.3655	9.7484	8.0019

Table (6): Effect of pH on the release of SA from NMC at different time intervals

3.6 Effect of pH and Time on release behaviour SA from NMC-g-PVA:



Figure(11): Cumulative release of SA release of NMC-g-PVA

Time (min)	Weight of SA (ug)				
	pH=3	pH=4	pH=5	pH=6	pH=7
0	0.709	9.7484	2.4888	0.1261	3.1741
5	5.2632	12.4538	11.6662	6.7694	7.112
10	6.0508	12.3515	10.229	7.8663	7.9686
15	6.3244	12.3158	10.8453	8.5158	7.9329
20	5.8105	11.6995	9.7841	8.5189	7.8663
25	5.7772	11.6329	9.0631	8.1042	7.8306
30	5.6391	11.6995	8.8252	8.4135	7.8306
35	5.4345	11.8375	8.5492	8.2755	7.8473
40	5.2965	11.3235	7.9329	8.3445	7.7973
45	5.0586	11.8042	7.5926	7.8663	7.626
50	4.8182	12.4538	7.0787	7.695	7.8663
55	4.5089	12.3515	6.9074	7.4546	8.0019
60	4.4756	12.4205	6.4957	7.25	8.2086

Table (7): The release behaviour of SA from NMC-g-PVA in various buffer

The results of pH and time study on the release of SA from NMC-g-PVA are shown in Table (7). The hydrogel displayed interesting releasing results indicating that it is highly sensitive to the pH environment. A bulk release of SA was noticed at pH 4. A significant release was observed in all other pH studied. A constant release of SA from NMC-g-PVA was detected throughout the time of study at all pH. This shows the time independent release nature of NMC-g-PVA compared to other two polymer matrices.

3.7 Assessment of Drug Releasing Capacity of Chitosan and its Derivatives:

The SA release studies in various buffer solutions indicated that CS, NMC & NMC-PVA are effectively releasing SA at pH 7, 6 & 4 respectively. Efforts were made to study the amount of SA released at these pH for various intervals of time at room temperature.

A comparative behaviour of the three polymer matrices are presented in table (8) & pictorially represented in fig (12). The rate of release of SA by CS found to increase with time span studied. The release of SA by NMC slowly increase and attained equilibrium release at 35mins, there after the release was constant. PVA grafted NMC immediately released SA at the initial stage of the study and attained equilibrium. The release was constant throughout the study.

Pharmacologically the sustained release of the drug is appreciated. Based on the release study the order of choice of the studied polymer matrix is :

NMC-g-PVA > NMC > CS

Thus, the modification of CS showed an improved performance as drug.

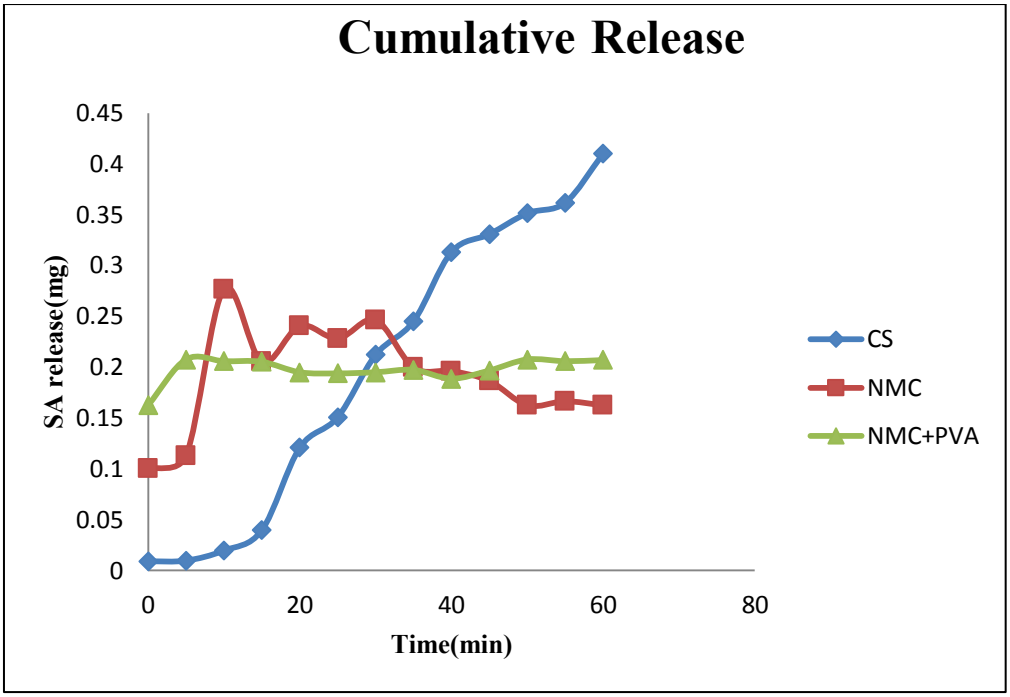


Fig (12) Cumulative release of SA from CS, NMC & NMC-g-PVA

Time(min)	Weight of SA in (mg)		
	pH=7	pH=6	pH=4
	CS	NMC	NMC+PVA
0	0.00904	0.10029	0.16247
5	0.009766	0.11282	0.20756
10	0.01963	0.2766	0.20585
15	0.03959	0.20526	0.20526
20	0.1208	0.24067	0.19499
25	0.1507	0.2281	0.19388
30	0.21204	0.24638	0.19499
35	0.24504	0.19959	0.19729
40	0.31314	0.19614	0.18872
45	0.33074	0.18646	0.19673
50	0.35133	0.16247	0.20756
55	0.36177	0.16647	0.20585
60	0.40984	0.16247	0.207

Table (8) Cumulative release of SA CS, NMC & NMC-g-PVA

3.8 Mechanism of Drug Loading and Releasing:

SA react with the amino group of glucosamine present in the CS chain. An amide linkage is formed between the amino group and a carboxylic group of SA with the liberation of water molecules. The presence of amide linkage in the SA loaded polymer matrix is confirmed by FT-IR studies. In NMC also SA was attached through amide linkages. There is a possibility formation of hydrogen bonding between a maleyl carboxylic group and OH group in SA. The hydrogen bonding stabilizes the entrapment of SA compared to CS. Due to the low energy state of the hydrogen bonded structure; it is readily formed giving 94% entrapment efficiency. The entrapment of SA is difficult due to the long chain PVA grafted in NMC-g-PVA, due to the steric hindrance; the amide formation is prevented leading to lower EE value than NMC. The comparative EE value with CS may be due to the physical entrapment of SA by the polymeric PVA chain. This is confirmed by the low intensity peaks of amide groups appeared in SA loaded NMC-g-PVA matrix, fig (12).

From the studies of drug release it is noted that CS matrix released SA with increasing rate with time at pH 7, NMC released with slow increase in rate and reached equilibrium at pH 6, and NMC-g-PVA released immediately and attained equilibrium at pH 4. SA is released from Chitosan by the hydrolysis of amide bond between SA and CS, which is a normal chemical reaction, found to increase with time. Therefore increase in release of SA was observed from CS matrix.

There is a possibility of hydrogen bonding between the entrapped SA and the maleyl group present in NMC. In the buffer solution there was a slow release of SA compared to CS matrix. This may be due to the hydrogen bonding along with amide bond in the matrix. The sudden release from NMC-PVA matrix may be due to the physical entrapment of SA on this matrix due to the long PVA chain hindrance.

SUMMARY AND CONCLUSION

Summary and Conclusion

In this research work entitled "**Evaluation of Chitosan Derivatives for the delivery of Salicylic Acid**" the natural, biocompatible Chitosan was modified into N-Maleyl Chitosan and Poly Vinyl Alcohol grafted N-Maleyl Chitosan. The formation and the chemical structure of the derivatives are confirmed by UV & FT-IR spectral studies. The presence of absorption due to n-π^* and π-π^* transitions in the UV spectra confirms the presence of maleyl group in Chitosan which is transparent to UV region.

The presence of absorption peak for C=C and C=N in NMC confirmed the modification of Chitosan into N-Maleyl Chitosan. The increase in the intensity of OH stretching vibration peak indicated the grafting of PVA in NMC matrix. The spectra of SA loaded polymers showed the characteristic peaks for CH stretching vibration of benzene ring and amide linkages, confirming the incorporation of SA into the matrices.

The thermal stability study of the three polymers indicated that NMC-PVA is most stable followed by CS and NMC which is least stable.

Salicylic acid is the drug used in skin ointments for the treatment of scaly patches, corns, calluses, and warts on the hands or feet. The literature survey indicated the need to identify an effective drug carrier for sustained SA release. SA was loaded in the above three hydrogel matrices. The calculation of EE reveal the order of EE as:

NMC>CS>NMC-PVA.

The suitable pH for the release of SA was determined by the release study experiments conducted in the pH range of 3-7. The studies revealed pH 7, 6 & 4 as suitable buffer for CS, NMC & NMC-PVA respectively. The release at pH 4 is suitable for skin treatments.

The variation of SA release with time was studied for all the pH range stated above, CS matrix released SA with increasing rate with time. NMC released at a slow rate and attained equilibrium rate after 40mins. SA was released immediately by NMC-PVA.

Based on the above study, a comparison of drug release by CS at pH 7, NMC at pH 6 & NMC-PVA at pH 4 was carried out. Among the three NMC may be a suitable carrier for SA at the required pH of the skin. The difference in behaviour of the three polymers is explained on the basis of amide bonding, hydrogen bonding and steric hindrance.

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