Dedicated to

Honourable Late. Shri. Chhotubhai Pithawala

Founder & President

Navyug Vidhyabhavan Trust, Surat.

Navyug Vidyabhavan Trust's
C. K. Pithawalla Institute of Pharmaceutical Science and Research, Surat - 395007

A Gesture to Profession

Father of Modern Pharmacy in India: Prof.M.L.Schroff

Prof. Mahadeva Lal Schroff or rightly called as Prof. M. L. Schroff is renowned for the title of pioneer and father of Indian Pharmacy Education. Prof. Schroff was not trained as a pharmacist but he remains an ideal to all pharmacy professionals for providing the right direction to pharmacy education in India.

Date of Birth: 6th March, 1902
Place of Birth: Darbhanga (Bihar), India
Educational Track:
School: Bhagalpur (Bihar)
College: Engineering College, Banaras Hindu University (BHU), Varanasi
Higher Education: Massachusetts Institute of Technology (MIT).
Popular as: Father of Modern Pharmacy in India.

Work Experience:

1929 – Took a job with Birla Brothers Ltd.
1932 – Joined Banaras Hindu University (BHU) as professor.
1934 – Introduced integrated 2-years B.Sc Course with Pharma Chemistry, Pharmacy and Pharmacognosy subjects at BHU.
1935 – Started United Provinces Pharma Association.
1937 – Introduced 3-years B.Pharm Course at BHU.
1939 – Started Indian Pharmaceutical Association with branches all over the country.
1940 – Introduced M.Pharm education at BHU.
1943 to 1949 – joined Birla Brothers as their Chief Chemist and Research Officer and served as Secretary to the Birla Laboratories.
1940 to 1950 – Selected as a member of scientific and government bodies, Indian Pharmacopoeial list committee, Health Panel of the Planning Commission etc.
1959 – Introduced courses like Diploma in Pharmacy, B Pharm, B Pharm (Hons.), and B.Sc with Pharmacology, Microbiology and Biochemistry.
1960 to 1964 – He was again taken up by the industry of Sahu Jain Group who placed him in charge of the Dharangdhara Chemical works at Tirunelveli, in Tamil Nadu. He served there for four years and introduced many new formulations and technical developments.
1964 to 1968 – Appointed as Head of Department at Jadhavpur University.
1966 – Elected as first president of Association of Pharmaceutical Teachers of India (APTI).
1965 to 1971 – Served as editor of Indian Journal of Pharmaceutical Education

Landmarks:

- Founder of the Indian Pharmacy Association (1935 as U.P.Pharma Association and 1939 as Indian Pharmacy Association),
- Indian Journal of Pharmacist (1945),
- Bhaishaj Patrika in Hindi (1980),
- Bheshjayan (1968),
- Indian Pharmaceutical Congress (1968),
- President of various States (Bengal, Bihar) Pharmacist Association
- President, Pharmacy Council of India (1954-1959)

In the honor of this legend personality IPA instituted a prestigious award "Prof. M.L. Schroff Medal", for students scoring the highest grades in the Final year B. Pharm. examinations amongst all the Universities and colleges in India. The award carries a certificate of merit, a medal and a cash prize of Rs. 1,000.

Let us take a pledge to carry this burning torch bright and unflickering.....

Academic Excellence

WINTER-2014 EXAM

- **Seventh Semester** – One student secured more than 8 SPI while nine students secured more than 7 SPI in Winter-2014 exam.
- **Fifth Semester** – Two students secured more than 8 SPI while eleven students secured more than 7 SPI in Winter-2014 exam.
- **Third Semester** – One student secured more than 8 SPI and four students secured more than 7 SPI in Winter-2014 exam.
- **First Semester** – Three students secured more than 8 SPI while nine students secured more than 7 SPI in Winter-2014 exam.

Meritorious Students

Class	Rank	Name of Student	SPI
Semester-VII	1	Vaghasiya Palak N.	8.00
	2	Vidiya Tanvika J.	7.47
	3	Mamrawala Hency H.	7.41
	4	Kadam Apeksha S.	7.41
Semester-V	1	Motwani Avinash	8.45
	2	Shah Mansi	8.09
	3	Patel Henisha	8.00
Semester-III	1	Qadri Misbah S.	8.35
	2	Shaikh Zebabibi Z.	8.02
	3	Indave Jaya B.	7.59
Semester-I	1	Patel Bansari B.	8.58
	2	Bamania Prem K.	8.36
	3	Vanecha Swati G.	8.15

SUMMER-2015 EXAM

- **Eight Semester** – One student secured more than 8 SPI while seven students secured more than 7 SPI in Summer-2015 exam.
- **Six Semester** – One student secured more than 8 SPI while eleven students secured more than 7 SPI in Summer-2015 exam.
- **Fourth Semester –** One student secured more than 8 SPI and five students secured more than 7 SPI in Summer-2015 exam.
- **Second Semester** – Four students secured more than 8 SPI while twenty one students secured more than 7 SPI in Summer-2015 exam.

Meritorious Students

Class	Rank	Name of Student	SPI
Semester-VIII	1	Shah Lajvi	8.03
	2	Vaghasiya Palak N.	7.73
	3	Kadam Apeksha	7.53
Semester-VI	1	Motwani Avinash	8.36
	2	Shikh Aamina	7.91
	3	Patel Henisha	7.73
Semester-IV	1	Shaikh Zeba	8.00
	2	Qadri Misbah	7.82
	2	Indave Jaya	7.82
	3	Patel Dhruv	7.36
Semester-II	1	Patel Bansari Bharatbhai	8.55
	2	Bamania Prem Kamlesh	8.33
	2	Patel Vyoma Tejasbhai	8.33
	3	Jangid Jyoti Harishbahi	8.15

GPAT Rankers

Academic Year 2014-15

Sr.No.	Name of Student	GPAT Score	All India Rank
1	Apeksha Kadam	159	547
2	Darshini Patel	152	878
3	Arpit Doshi	134	1799
4	Aditya Patwa	130	2088

Participation

❖ Conference/Seminar/Workshop attended by Faculty

- ✓ Dr. M.G.Saralaya attended (Resource Person, Chairman) 3rd International Conference on "Novel Polymeric Materials in Pharmacy and Engineering" at Shree Dhanvantary Pharmacy College-KIM on 12th March, 2015.
- ✓ Dr. Bhumika Desai attended seminar on "Nanotechnology-based drug delivery: Opportunities and Challenges" at Maliba Pharmacy College, Tarsadi on 11th April, 2015.
- ✓ Dr. Pinal Harde presented poster on **Preliminary Pharmacognostical studies of leaves of Lagerstroemia Speciosa** at 3rd International Conference on Novel Polymeric Materials in Pharmacy and Engineering at Shree Dhanvantary Pharmacy College-KIM on 12th March, 2015 and secured **Second** prize.
- ✓ Dr. Ashok Akabari presented poster on **Kinetic determination of Pitavastatin in acid media by HPTLC method** at 3rd International Conference on "Novel Polymeric Materials in Pharmacy and Engineering" at Shree Dhanvantary Pharmacy College-KIM on 12th March, 2015 and secured **First** prize.
- ✓ Mrs. Kavita Sutariya attended 3rd International Conference on "Novel Polymeric Materials in Pharmacy and Engineering" at Shree Dhanvantary Pharmacy College-KIM on 12th March, 2015.
- ✓ Dr. Ashok Akabari, Dr. Pinal Harde and Mrs. Kavita Sutariya attended GUJCOST sponsored one day Symposium on "Analytical Quality by Design: a Key Tool for Analytical Method Development and Validation" held at Maliba Pharmacy College, Uka Tarasadia University, Bardoli on 29th September, 2015.
- ✓ Mr. Amish Gandhi and Ms. Richa Champaneria attended "Festive De Pharma" at Maliba Pharmacy College, Tarsadi, Bardoli on 11th April, 2015.
- ✓ Mrs. Neha Prajapati attended GUJCOST and DST sponsored National workshop on "Animal handling and Dosing techniques in preclinical studies for Drug research" at A.R.College of Pharmacy & G.H.Patel Institute of Pharmacy, Anand on 09th-10th April, 2015.
- ✓ Ms. Prakruti Jadav attended GUJCOST and DST sponsored National workshop on "Animal handling and Dosing techniques in preclinical studies for Drug research" at A.R.College of Pharmacy & G.H.Patel Institute of Pharmacy, Anand on 09th-10th April, 2015.
- ✓ Ms. Richa Champaneria attended GUJCOST and DST sponsored National workshop on "Animal handling and Dosing techniques in preclinical studies for Drug research" at A.R.College of Pharmacy & G.H.Patel Institute of Pharmacy, Anand on 09th-10th April, 2015.
- ✓ Ms.Hiral Patel attended "APOCALYPSE-2015" at K.B.Institute of Pharmaceutical Education & Research, Gandhinagar on 7th & 8th August, 2015.

❖ Conference/Seminar/Workshop attended by Students

- ✓ Thirty two students from second and sixth semester participated in various competitions like poster presentation, case study, marketing, bookies, oral presentation, model presentation, scitoons, debate etc. at state level "Festive De Pharma" organized by Maliba Pharmacy College, Tarsadi on 10th March,2015. Students got:
  I st Prize (Model Presentation-**Digestive and Urinary System**): Patel Bansari, Patel Vyoma, Lohia Naman, Rangwala Yasmin, Baria Niketa
  II nd Prize (Bookies): Motwani Avinash, Dimple Patel
  II nd Prize (Pharma Quiz): Patel Henisha, Limbachiya Dhruv, Kotadiya Vikas, Patel Dimple

- ✓ Fourteen students from eighth semester attended 3rd International Conference on "Novel Polymeric Materials in Pharmacy and Engineering" at Shree Dhanvantary Pharmacy College-KIM on 12th March,2015 from which Mr. Malankiya Dipak (8th Sem student) presented a poster on **Development and validation of analytical method for simultaneous determination of Atorvastatin and Irbesartan in synthetic mixture.**

- ✓ Twenty six students from second and fourth semester attended GUJCOST and DST sponsored National workshop on "Animal handling and Dosing techniques in preclinical studies for Drug research" at A.R.College of pharmacy & G.H.Patel Institute of Pharmacy, Anand on 09th-10th April, 2015. Students got:
  I st Prize (Model Presentation): Bamania Prem, Chandla Sapna, Patel Vrushti
  II nd Prize (Model Presentation): Lohia Naman, Patel Bansari, Patel Vyoma, Rangwala Yasmin, Baria Niketa
  III rd Prize (Model Presentation): Bheda Hurma, Motwani Kunal, Patel Jay, Shaikh Quaratulain

- ✓ Thirteen students from third semester attended "APOCALYPSE-2015" and participated in various competitions like powerpoint presentation, model presentation, bookoholic, it's my product, quiz competition, pharma advertisement, capture it, etc. at K.B.Institute of Pharmaceutical Education & Research, Gandhinagar on 7th & 8th August, 2015.

❖ Upcoming Events

- ✓ **National Seminar on Recent Advances in Natural Products Chemistry for Drug Discovery** at Department of Chemistry, Netaji Subhash Mahavidyalaya, Udaipur, Tripura on 28th & 29th November, 2015.

- ✓ **48th Annual conference of Indian Pharmacological Society** at Rajkot, Sourastra, Gujarat from17th to 20th December, 2015.

- ✓ **67th Indian Pharmaceutical Congress** on 19th, 20th and 21st December, 2015 held at JSS University, Sri Shivarathreeshwara Nagar, Mysuru-570015.

- ✓ **NIPiCON 2016 – International Conference** at Institute of Pharmacy, Nirma University, Ahmedabad from 23rd to 25th January, 2016.

- ✓ **22nd ISCB International Conference on Recent Trends in Affordable and Sustainable Drug Discovery and Developments** at Uka Tarsadia University, Bardoli from 6th to 8th February-2016.

Guest Lectures

- A guest lecture on a topic of **"Scope and future prospectus at abroad"** by Mrs. Rajani Purohit and Mr. Richie Christie from Edwise International Institute, Surat, was organised on 2nd January, 2015.
- A guest lecture on a topic of **"Awareness on SAS for Pharmacy Students"** by Mr. Manish Soni and Mr. Hiren Barchha from Epoch Research Institute India Pvt. Ltd, Ahmedabad, was organized on 09th January, 2015.
- A guest lecture on a topic of **"Consumer Protection Act"** by Mr. S.D.Tambawala (Ex. Assistant controller, Legal Metrology & Consumer, Surat) and Mr. Chetan Tailor was organised on 19th March, 2015.
- A lecture on a topic of **"Career after B.Pharm in India – Higher Studies & Job Opportunities"** by Ms. Shivali Desai, Lecturer, CKPIPSR, was organized on 30th June, 2015.
- A guest lecture on a topic of **"Career Guidance & Career Counselling (MBA)"** by Prof. Dr. Pradip manjrekar, Dean of Business Management Department, D.Y.Patil University, Navi Mumbai, was organized on 1st August, 2015.
- A guest lecture on a topic of **"Managing health in present life style"** by Dr. Devangi Jogal and Mr. Nilesh Jogal from Jogi Ayurvedic Hospital, Surat, was organized on 5th August, 2015.
- A guest lecture on a topic of **"How to crack GRE – a career option after graduation"** by Mr. Gautam Surana, Central Director, Endeavor Careers, Mumbai, was organised on 8th September, 2015.
- A guest lecture on a topic of **"Pharmacy and Pharmacy Career"** by Mr. Bimal Vyas and Mr. Hiral Trivedi, Eris Life Science Pvt. Ltd., Ahmedabad, was organized on 10th September, 2015.
- A guest lecture on a topic of **"Pharmacy and Pharmacy Career"** by Mr. Aravind Warrier and Mr. Amitkumar Das, Novo Nordisk India Pvt. Ltd., Bangluru, was organized on 16th September, 2015.

Events Organized

"BLOOD DONATION CAMP" & "THALASSEMIA CHECKING PROGRAM"

Blood Donation Camp and Thalassamia Awareness Program was held at our institute on 21st November, 2014 by coordination of Indian Red Cross Society. Seven students donated blood. A lecture on Thalassemia was given by Dr. Mukeshbhai Jagiwala as a part of Thalassamia Awareness Program.

"GANDHI NIRVAN DIN"-swachhata abhiyan

To the view to support the movement of "Swatch Bharat Abhiyan", our institute celebrated "Gandhi Nirvan Din" on 30th January, 2015. Students enthusiastically participated in the cleanliness, speech on "Clean India" and drawing competition. At the end of event, oath was taken to keep our India clean.

"INTERNATIONAL WOMEN'S DAY"

In view to the International Women's Day celebration, our institute had organized a seminar on different topics such as "importance of international women's day celebration", "women empowerment", "self defense among women", and "professional etiquettes and dressing for women", on 26th February, 2015 to educate the women faculty members and girls students about women's rights and safety of herself.

"INTERNATIONAL YOGA DAY"

Our organization arranged a special workshop on yoga for two days, 18th and 19th June, 2015. Different "Yogasans", "Bhramari", "Pranayam", etc. were performed by all faculty members and students under the guidance of Mr. Manish Pastagia, an Art of Living trainer.

"WOMEN EMPOWERMENT FORTNIGHT"

Different days namely Mahila Suraksha Divas, Mahila Arogya Divas, Mahila Shikshan Divas, Mahila Balposhan Jagruti Divas, Mahila Kanuni Jagruti Divas and Mahila Sharirik Saushthav Divas were celebrated by arranging seminar, drawing competition, elocution competition as well as one hour yoga session during 14 days from 01/08/15 to 14/08/14.

"PLACEMENT"

Placement drive for students of 7th semester was oraganised (10th and 16th September, 2015) by Eris Life Science Pvt. Ltd., Ahmedabad and Novo Nordisk India Pvt. Ltd., Bengaluru. In this event, Mr.Amitkumar Das, Director HR gave a lectures on topics "Path of Novo Nordisk and its Success Stories, "Path after Pharmacy Graduation" and Mr.Bimal Vyas, Senior Manger HR (Eris Life Sciences) had given a talk on "Career in Pharma Marketing and its career challenges". Which after followed by various evaluation for reqruitment of final year B.Pharm student. In the primary selection 8 (Eight) students were selected and will join their job after completion of their course. Mangement, Principal and faculties congratulated the students.

Hobby Corner

A NEW AND GOLDEN COLLEGE LIFE.

School days are gone,
And college days are here

Scream, shout and enjoy
As these days,you'll ever enjoy

Jorney of twelve long years
Have came to an end.

And here we stand
on the gates of new trend.

its time to leave
old friends and foes

as we see new people
and few faces to explore

the process of studies
will go on forever

but this college life,
will not be forever

time will pass by,
and days will end.

Time to leave a college
Will be have again

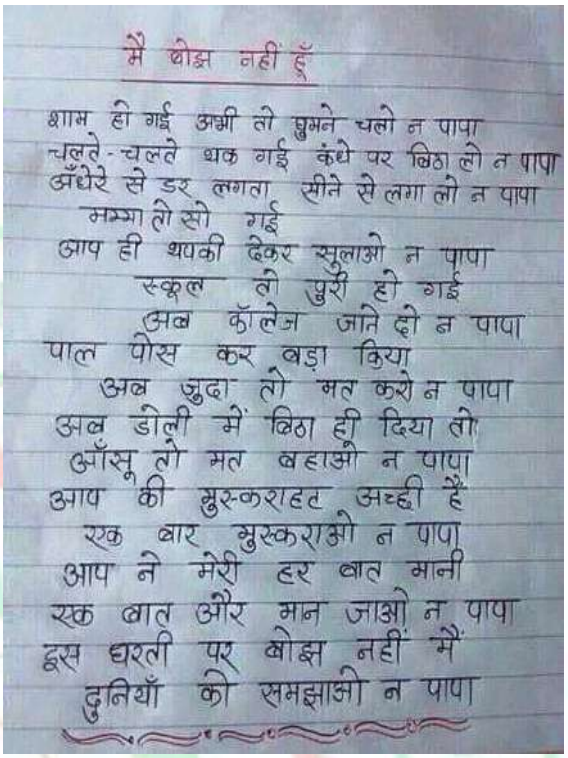
Again a new life,
Will wait ahead

As we avoid farewell
To these golden days

So live this moment,
As its not going to stay.

Life is precious treasure
whose one stage are "college days"

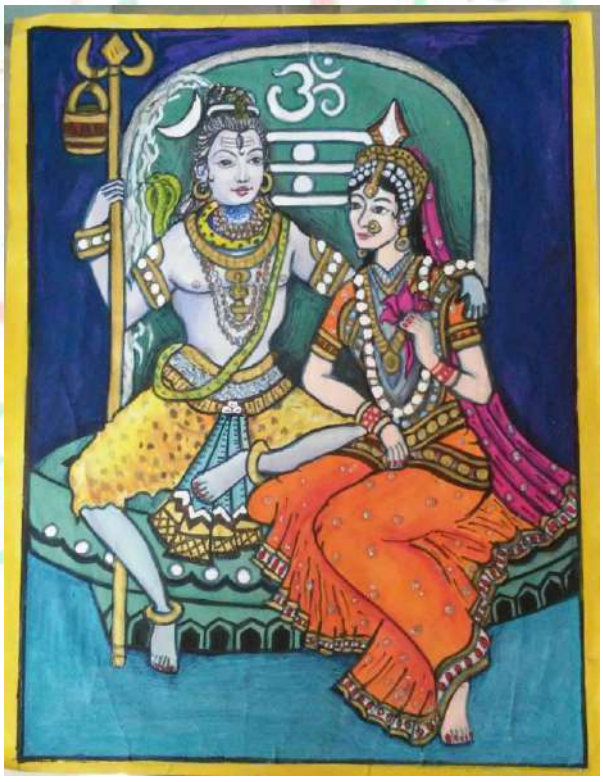
— Poem by Shivam Jha
(3rd Sem, B.Pharm)



मैं बोझ नहीं हूँ

शाम हो गई अभी तो घुमने चलो न पापा
चलते-चलते थक गई कंधे पर बिठा लो न पापा
अँधेरे से डर लगता सीने से लगा लो न पापा
मम्मा तो सो गई
आप ही थपकी देकर सुलाओ न पापा
स्कूल तो पुरी हो गई
अब कॉलेज जाने दो न पापा
पाल पोस कर बड़ा किया
अब जुदा तो मत करो न पापा
अब डोली में बिठा ही दिया तो
आँसू तो मत बहाओ न पापा
आप की मुस्कराहट अच्छी है
एक बार मुस्कराओ न पापा
आप ने मेरी हर बात मानी
एक बात और मान जाओ न पापा
इस धरती पर बोझ नहीं मैं
दुनियाँ को समझाओ न पापा

— Poem by Nidhi Chitte.
(3rd Sem, B.Pharm)



— Painting by Prem Bamania.
(3rd Sem, B.Pharm)

INDUSTRIAL EXPERIENCE

Dear Sir/Mam,

Myself Bhavi Patel (M.Pharm in Pharmacology). I recently joined C.K. Pithawalla Institute of Pharmaceutical Science and Research, Surat as a lecturer. I had done my project work of M.pharm at Cadila Pharmaceutical Limited, Dholka, Ahmadabad. I was very new for that multinational company's environment at that time and what made me write this is that feeling of nervousness and confusion as a fresher in industry. So here I am sharing my industrial experience as a trainee in pharmaceutical company, hoping that this will helpful to other students.

The Cadila Pharmaceutical Limited is an Indian based private multinational company who provide branded and generic formulations, APIs, Contract research and contract manufacturing. The Dholka plant has several departments like manufacturing unit, R&D (Research and development), F&D (formulation and development), clinical trial department, analytical department, QA (Quality assurance) department etc. I was in CRO(Contract Research Organization) of R&D department as trainee for 6 months where they are conducting bioequivalence study. The CRO again divided into 4 units: Screening area, CPPU(Clinical Pharmacology and Pharmacokinetic Unit), QC (Quality Assurance) and Bioanalytical department.

Various questions may arise in your mind that what is bioequivalence study? Why it is needed? Why this much amount of investments are provided to such kind of study? Let me explain you in simple terms, the bioequivalence is a term in pharmacokinetic used to assess the expected in vivo equivalence of two formulation having same active ingredient. The two products are bioequivalent if they are pharmaceutical equivalent and their bioavailabilities (rate and extent of drug absorption) after administration in the same molar dose aresimilar to such a degree that their effect, with respect to efficacy and safety,can be expected to be essentially the same. If a new molecule or new drug (called brand name drug) introduce 1st time in market by some company, they have marketing authorization of that drug for 20 years under patent protection. But after expiration of that patent period of 20 years, any companies can manufacture and market the copies of brand name drug called generic drug by filing ANDA application. The main purpose of introducing generic drugs is to provide cheaper substitute of the brand name drug having same quality and efficacy thus reducing the overall healthcare cost of the country.

In 1984, United State Congress passed the "Drug Price Competition and Patent Term Restoration Act of 1984" also called as Hatch-Waxman Act that authorized FDA to approve generic drug products through BA and BE studies. As a result of this act, several activities were initiated by the FDA for the review and approval of generic drug application (Abbreviated New Drug Application, commonly known as ANDA). This act is dealing with the approval from FDA, market exclusivity, rights of exclusivity, patent term extension and orange book listing. America's Hatch- Waxman legislation included a section, now known as the "Bolar Provision", that allowed the importation of the small amount of raw material required to prepare the compound and test a drug product before the patent expiration so that the generic version would be available for marketing immediately a patent expired. Consequently on the basis of simple pharmacokinetic concepts and parameters, bioavailability and bioequivalence studies have been established as accepted surrogates for expensive, complicated and lengthy clinical trails, and are used worldwide to establish and ensure consistent quality and a reliable, therapeutically effective performance of marketed dosage forms.

Talking about the procedure of bioequivalence study, the human volunteers are screened and enrolled in the study. They stay in the CPPU unit during the entire study period. Half of the volunteers receives brand name

drug and half receives the investigational drug. The treatments allocated to them are according to the randomization schedule prepared by software. Blood samples of volunteers are collected at different time point mentioned in the protocol and the plasma drug concentrations of both drugs are measured using various analytical techniques. Finally the comparison of plasma drug concentration verses time curve of both formulations is done. After calculating the statistical parameters, biostatistician decides whether the two formulations are bioequivalent or not.

I personally feel that the documentation work in industry is of a great importance because that particular document that you had signed represents your work. All activities are performed round the clock under the direct observation of QA personals; even each and every second are counted. As a pharmacist, one must know that pharmacies in industry are access control area. Only pharmacist appointed by industry, head of department and QA persons has access to the pharmacies .The pharmacist must have skill to handle the packing, labeling and dispensing of drugs with emphasis on storage condition of drugs and he must be accurate in documentation work.

My overall experience in industry was great even I also experienced the US-FDA audits. I feel that everyone shouldexperience it once then only we can understand the things we are studying in the books. I suggest the fresher or to be fresher in industry that be confident in your work, be dedicated to your work, never do false documentation, do not lie about your work and manage to have good relation with your colleges. I think that's enough to lead you on the path of success.

– **Miss. Bhavi Patel (Lecturer, Dept.of Pharmacology,CKPIPSR, Surat.)**

Extra-Curricular Activities

Number of extra-curricular activities including Sports week celebration, Teacher's day celebration, Industrial tour and visit, Days celebration, Annual Function celebration, NSS Activities (Tree Plantation, Campus Cleaning), various competitions like Mehndi, Drawing, Bookies, Quiz, Foody Funda, Rangoli, Singing, Weight lifting, Push ups, Debate were organized by institute during academic Year 2015.

Sports Week Celebration

Days Celebration

Industrial Visit & Tour

Editor's Desk

It gives me an immense pleasure to present before you the latest issue of CKPIPSR e-newsletter. The Pharmacy profession is undergoing rapid change, pharmacist is no longer a mere dispenser of drugs but has assumed a more crucial role in medicine management and as overall health care programmer to face global challenges. The CKPIPSR e-news Bulletin provides the platform to pharma fraternity to contribute/update the knowledge of recent developments in pharmaceutical sciences and represent the gleaming achievements. We welcome your inputs for future newsletters and urge you to stay connected with us through email.

Email ID: ckpipsr@gmail.com.

Review Article

Recent Innovation in Nanotechnology: Nanogel

Dr. Mahesh G. Saralai, Mrs. Mitali M. Patel*

Department of Pharmaceutics, C.K.Pithawalla Institute Of Pharmaceutical Science and Reserch, Dumas Magdalla Road,Surat-395007,India.

ABSTRACT

Nanogels have shown a great potential for the delivery of large number of drugs to different organs of the body owing to their high biocompatibility, high drug loading capacity, high biodegradability (and hence low cytotoxicity), good permeation capabilities and tissue mimicking properties. Their high water retention makes them ideal capable of incorporation of bulky drugs like proteins, peptides, oligonucleotides and other macromolecules. All these properties of nanogels make them able to carry number of drugs to vast number of organs. Nanogels have shown potential in many fields including chemotherapy, diagnosis, organ tergeting, gene delivery and many others. The main areas of the target for the nanogels have been tumors of brain, liver, skin etc. Other uses of the nanogel are in diabetes, inflammation, wound healing, local anesthesia etc. This review concentrates over the targeting potential of nanogels in different organs for various conditions.

KEYWORDS: Nanogel; Polymer; Swelling; Loading capacity; Organ targeting; Cancer therapy.

Introduction

Nanogels are potential polymeric nanoparticulate systems having tremendous biomedical applications that can offer time-controlled drug delivery as well as active drug targeting. Structurally nanogels are spherical shaped nanometer sized (10s-100s of nm i.e., upto about 700 nm) Hydrogels also known as hydrogel nanoparticles possessing an internal polymeric network for incorporation of drug molecules or other biomolecules. Nanogels arecomposed of synthetic polymers or biopolymers which are chemically or physically cross-linked. They have been largely studied for the incorporation and release behavior of bioactive molecules e.g., drugs, peptides, proteins, antigens oligonucleotides, genes, carbohydrates, DNA etc. and also for the incorporation of inorganic molecules e.g. quantum dots,silver nanoparticles, magnetic nanoparticles etc. Nanogels can be precisely tuned to increase their circulation time in the blood,avoid clearance by the reticuloendotheial system and hence prolong the drug release and can be conjugated with other molecules for targeted delivery of drugs that release the active substances at the targeted site.Nanogels can be administered with two basic strategies viz. passive targeting and active targeting. Drug release from nanogels follow mechanisms based on above two strategies. In case of passive targeting the nanogels show drug release with respect to their surface charge, size, swelling and other physico-chemical properties.

In case of active targeting nanogels are conjugated with some specific moieties that specifically recognize and bind to some of the receptors that are over expressed at the target sites e.g., in case of tumors many types of receptors are overexpressed that leads to the accumulation of conjugated nanogels at the target site.

Nanogels can imbibe large amounts of water and swell to large volumes that increase their loading capacity to accommodate a large quantity of drug. Fig. 1 shows the general structural network of nanogel and their drug loading capacity. With nanogels it is possible to attain greater than 98% of loading efficiency. Since nanogels are basically hydrogels so another unique property that they shear is their tissue mimicking ability to the large amount of water they contain and the biocompatible materials used in their preparation. Topical application of such type of a gel gives a soothing effect that is very effective in treatment for conditions like wounds. Among some other outstanding properties of the nanogels is their self-healing ability wherein new bonds in them spontaneously form upon thebreakage of the older bonds.

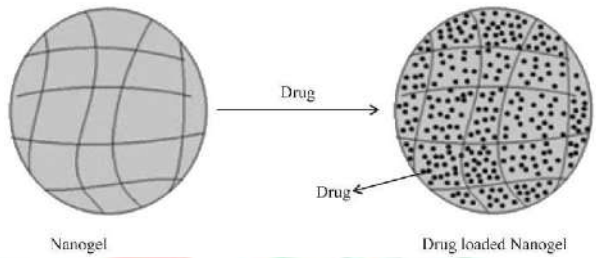


Fig. 1. Polymer network of nanogel demonstrating high drug loading capacity.

Advantages of Nanogels

Nanogels are quite smart to carry drugs to the biological sites of actions besides offering several other advantages ranging from drug loading to the pharmacokinetic characteristics. Nanogels are known for their high drug loading capacities and controlled release regulated by varying crosslinking densities of the polymers used in the preparation of the nanogels that affect the swelling characteristics of nanogels. Following are some of the advantages that make nanogels unique as delivery systems:

a) Highly biocompatible (due to high water content and hence behave like natural tissue) and therefore immunological responses
b) Biodegradable, that makes these nanocarriers nontoxic
c) High drug loading capacity
d) Easily escape entrapment by reticuloendothelial system

e) By tuning crosslinking densities drug release can be regulated
f) Better permeation via biological membranes due to extremely small size
g) Can incorporate both hydrophilic and hydrophobic drugs and charged solutes
h) Excellent transport characteristics.

PROPERTIES OF NANOGELS

Biocompatibility and degradability

Nanogel based drug delivery system is highly biocompatible and biodegradable due to this characteristics it is highly promising field now a days.

Swelling property in aqueous media

The most beneficial feature of Nanogels is their rapid swelling/de-swelling characteristics.

Higher drug loading capacity

The properties of higher drug loading capacity of nanogels depend on the functional group present in the polymeric unit. These functional groups have a tremendous effect on drug-carrying and drug-releasing properties, and some functional groups have the potential to conjugate with drugs/antibodies for targeting applications.

These pendent functional groups of polymeric chains contribute toward establishing hydrogen bonding or van der Waals forces of interactions within the gel network and thus facilitate the drug-carrying efficiency. Moreover, the presence of functional groups at interface with drug/protein molecules is also responsible for higher loading.

Particle size

Nanogels typically range in size of 20–200 nm in diameter and hence are effective in avoiding the rapid renal exclusion but are small enough to avoid the uptake by the reticuloendothelial system.

Good permeation capabilities due to extreme small size. More specifically, it can cross the blood brain barrier (BBB).

Solubility

Nanogels are able to solubilize hydrophobic drugs and diagnostic agents in their core or networks of gel.

Electromobility

Nanogels could be prepared without employing energy or harsh conditions such as sonication or homogenization, which is critical for encapsulating biomacromolecules.

Colloidal stability

Nanogels or polymeric micellar nanogel systems have better stability over the surfactant micelles and exhibit lower critical micelle concentrations, slower rates of dissociation, and longer retention of loaded drugs.

Non-immunologic response

This type of drug delivery system usually does not produce any immunological responses.

Others

Both type of drugs (hydrophillic and hydrophobic drugs and charged solutes) can be given through nanogel. Such properties of nanogel are significantly influenced by temperature, presence of hydrophilic/ hydrophobic groups in the polymeric networks, the cross-linking density of the gels, surfactant concentration, and type of cross-links present in the polymer networks.

DRUG RELEASE FROM NANOGEL FORMULATION

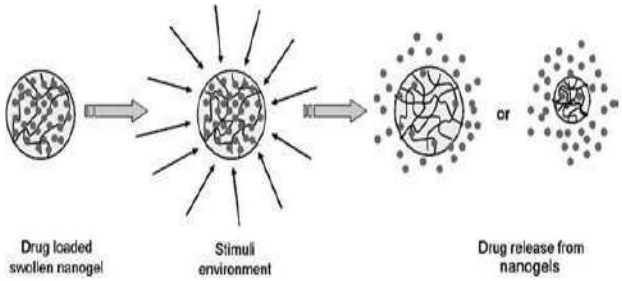


Fig 2: Drug Release from nanogel

DISADVANTAGES OF NANOGELS

a) Expensive technique to completely remove the solvent sand surfactants at the end of preparation process.
b) Surfactant or monomer traces may remain and can impart toxicity.

CLASSIFICATION OF NANOGELS

Nanogels are more commonly classified into two major ways. The first classification is based on their responsive behavior, which can be either stimuli-responsive or non-responsive.

1. In the case of non-responsive microgels, they simply swell as a result of absorbing water.
2. Stimuli-responsive microgels swell or deswell upon exposure to environmental changes such as temperature, pH, magnetic field, and ionic strength.

Physical cross-linked gels

Physical gels or pseudo gels are formed by weaker linkages through either (a) van der Waals forces, (b) hydrophobic, electrostatic interactions, or (c) hydrogen bonding. A few simple methods are available to obtain physical gels. These systems are sensitive and this sensitivity depends on polymer composition, temperature, ionic strength of the medium, concentrations of the polymer and of the cross-linking agent. The association of amphiphilic block copolymers and complexation of oppositely charged polymeric chains results in the formation of micro- and nanogels in only a few minutes. Physical gels can also be formed by the aggregation and/or self-assembly of polymeric chains.

Liposome Modified Nanogels

Kono *et al.,*have disclosed liposomes bearing succinylated poly(glycidol)s; these liposomes undergo chain fusion below pH 5.5 that has been shown to efficiently deliver calcein to the cytoplasm. Liposomes anchored by or modified with poly(*N* isopropylacrylamide)-based copolymeric groups are suitable for thermo- and pH-responsive nanogels, which are being investigated for transdermal drug delivery.

Micellar Nanogels

Polymer micellar nanogels can be obtained by the supramolecular self-assembly of amphiphilic block or graft copolymers in aqueous solutions. They possess unique core-shell morphological structures, where a hydrophobic block segment in the form of a core is surrounded by hydrophilic polymer blocks as a shell (corona) that stabilizes the entire micelle. The core of micelles provides enough space for accommodating

various drug or biomacromolecules by physical entrapment. Furthermore, the hydrophilic blocks may form hydrogen bonds with the aqueous media that lead to a perfect shell formation around the core of micelle. Therefore, the drug molecules in the hydrophobic core are protected from hydrolysis and enzymatic degradation. Researchers (Li *et al.,* 2006) successfully developed highly versatile *Y*-shaped micelles of poly(oleic acid-*Y*-*N*-isopropylacrylamide) for drug delivery application. In this study, the delivery of prednisone acetate above its lower critical solution temperature (LCST) was demonstrated. A representation of micelle formation is shown in Figure.

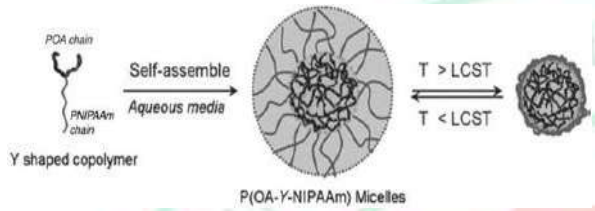


Fig. 3: *Y*-shaped copolymer self-assembly to give micelle structures.

Hybrid Nanogels

Hybrid nanogels are defined as a composite of nanogel particles dispersed in organic or inorganic matrices. Group of studies have demonstrated nanogel formation in an aqueous medium by self-assembly or aggregation of polymer amphiphiles, such as pullulan-PNIPAM, hydrophobized polysaccharides, and hydrophobized pullulan. This group has investigated cholesterol-bearing pullulan (CHP) nanogels. These nanogels have the ability to form complexes with various proteins, drugs, and DNA; and it is even possible to coat surfaces of liposomes, particles, and solid surfaces including cells (Nishikawa *et al.,* 1996; Kuroda *et al.,* 2002).These hybrid nanogels are also capable of delivering insulin and anticancer drugs more effectively. CHP is composed of pullulan backbone and cholesterol branches. The CHP molecules self aggregate to form mono-dispersed stable nanogels through the association of hydrophobic groups that provide physical cross-linking points as shown in Figure

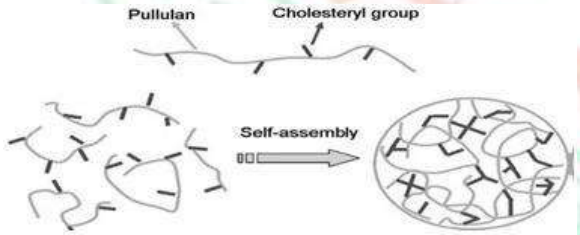


Fig. 4: Schematic representation of CHP nanogel preparation by physical cross-linking (self-assembly).

Chemically cross-linked gels

Chemical gels are comprised of permanent chemical linkages (covalent bonds) throughout the gel networks. The properties of cross-linked gel system depend on the chemical linkages and functional groups present in the gel networks. Different nanogels have been synthesized using different strategies for chemical linking of polymeric chains. Usually, hydrophilic polymers and hydrophilic–hydrophobic copolymers are obtained by the polymerization of vinyl monomers in the presence of multifunctional cross-linkers that are the launch cross-linking points within and between the polymeric chains. These cross-linking points allow modifying entire physicochemical properties of the gel systems.

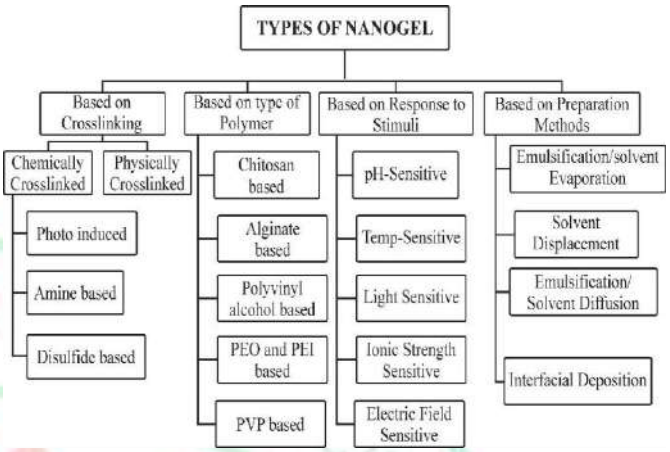


Fig 4: Type of Nanogel

Method of Preparation of Nanogel:

Fig 5: Schematic representation of method of preparation

SYNTHESIS OF NANOGELS

Photolithographic techniques

Photolithography has been explored to fabricate 3D hydrogel particles and microgel or nanogel rings for drug delivery. The photolithographic method requires the development of techniques for surface treatment of stamps or new materials for replica molds to permit the release of molded gels from stamps or replica molds. photolithography consists of five steps. In the first step, the UV cross-linkable polymer, which possesses low surface energy, as a substrate is released on the pre-baked photo resist-coated water. The next step involves molding the polymer into patterns on the silicon wafer by pressing the quartz template onto the polymer and exposed it to the intense UV light.

In the third step, the particles with a thin residual interconnecting film layer are uncovered by removing the quartz template. Subsequently, this residual thin layer is removed by a plasma containing oxygen that oxidizes it. In the last step, the fabricated particles are directly collected by dissolution of the substrate in water of buffer.

Table 1: Method of Preparation of Nanogel

Method	Composition
Ionic gelation	Chitosan, TPP
Emulsion polymerization	NIPAM, MBA Aac
	NIPAM, MAA, PEGMA
	AMPS, NIPAM, PEG
Surfactant free emulsion Polymerization	NIPAM, BA
Solvent emulsification/ evaporation method	NIPAM
Solvent displacement method (or nano-precipitation)	Tri block PLA-
	PEG-PLA
	Copolymers
Inverse nanoprecipitation	Polyglycerol,
Modified solvent displacement method	Copolymer
Emulsion-solvent evaporation technique	PEI, PEG
Semi-continuous emulsion polymerization	MAA-EA linked
	with DAP, PVC,
Precipitation polymerization	NIPAM,
Desolvation method	Carbopol 940,
Emulsion-droplet coalescence method	Cabopol 940
Microemulsion template method	Carbopol 940,
	Cetylpalmitate,
Free radical precipitation polymerization	NIPAM, Acrylic acid (AA)
Dispersion polymerization	PEG, Oligo

They can be classified into four categories: waterin-oil (W/O) heterogeneous emulsion, aqueous homogeneous gelation, spray drying method, and chemical cross linking of Dex.

WATER-IN-OIL (W/O) HETEROGENEOUS EMULSION METHODS

W/O emulsion methods involve generally two steps: emulsification of aqueous droplets of water soluble biopolymers in continuous oil phase with an aid of oil-soluble surfactants and cross linking of biopolymers with water-soluble cross linkers.

Chitosan (CS), hyaluronan (HA), and Dex are naturally occurring carbohydrate-based biopolymers. Many methods have been developed for the preparation of microgels of these biopolymers.

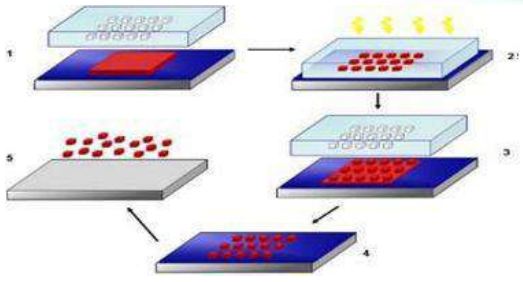


Fig 6: Schematic diagram of five steps involved in photolithography

Inverse (mini) emulsion method

A W/O emulsion is formed from a mixture consisting of aqueous biopolymer droplets and a continuous oil phase using either a homogenizer or a high-speed mechanical stirrer.

Fabrication of biopolymers

Resulting aqueous droplets of biopolymers are then crosslinked with appropriate crosslinking agents. Then crosslinked microgel particles are prepared as dispersion in organic solvents purified by precipitation, centrifugation, washing with organic solvents such as isopropanol, and lyophilization. The size of the prepared microgel particles can be controlled by amount of surfactants and crosslinking agents as well as stirring speed during the formation of inverse emulsion.

Example: preparation of HA-based microgels, carboxylic acids of HA were crosslinked with adipic dihydrazide (ADH) as a crosslinker in the presence of ethyl-3-[3-dimethylamino]propyl carbodiimide (EDCI) in aqueous droplets.

Reverse micellar method

Similar to the inverse (mini) emulsion method, the reverse micellar method also involves a W/O dispersion; however, a relatively large amount of oil-soluble surfactants is used to form a thermodynamically stable micellar solution consisting of aqueous droplets dispersed in the continuous oil phase .The resulting micellar droplets have a submicron size ranged from tens to hundreds of nanometers in diameter.

Tumor targeted CS-based nanogels were prepared in inverse microemulsion of hexane containing Aerosol OT as a stabilizer in the presence of doxorubicin (Dox)-modified Dex. Aqueous glutaraldehyde was used to crosslink CS. The resulting Dox-encapsulating CS-based nanogels have a diameter of around 100nm.

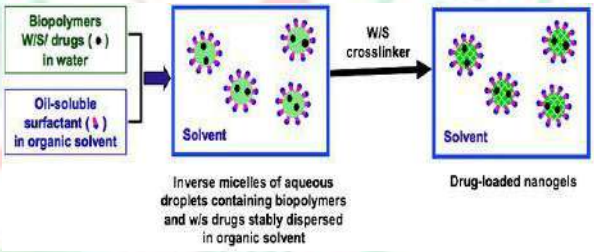


Fig. 7: Illustration of the reverse micellar method for the preparation of nanogels.

Membrane emulsification

In the membrane emulsification technique, the to-be-dispersed phase is passed through the membrane (glass or ceramic), which possesses uniform pore size. Under certain conditions the emulsion droplets or microgels with specific morphology are formed on the surface of the membrane and afterwards, with a continuous phase that is flowing across the membrane, these fabricated emulsion droplets or microgels are recovered (Nakashima *et al.,* 2000). These fabricated emulsion droplets can be in different emulsion formation such as water-in-oil (W/O), oil-in-water (O/W), oil-in-water-in-oil (O/W/O), and water-in-oil-in-water (W/O/W) (Oh

et al., 2008b). The size of the formed droplet is controlled by the membrane pore size, velocity of the continuous phase, and pressure of the trans-membrane. Figure 8 represents the diagram using this synthesizing technique.

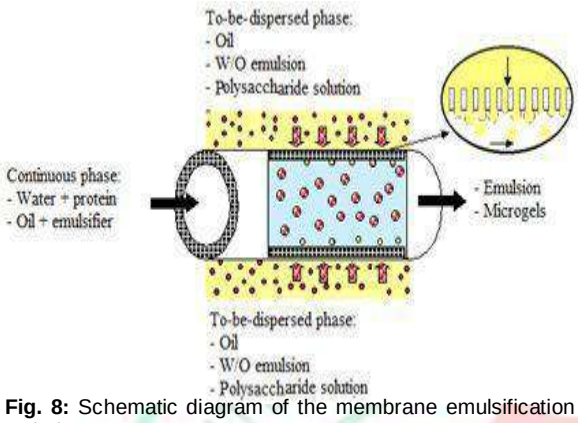


Fig. 8: Schematic diagram of the membrane emulsification technique.

Chemical cross linking

Biodegradable Dex-based microgels and hydrogels were prepared by various methods based on chemical cross linking including Carbodiimide coupling, Michael addition reaction, Free radical polymerization.

Carbodiimide coupling

Novel pullulan chemistry modification

Synthesis of cholesterol based pullulan nanogel (CHP) was done by reacting mixture of cholesterol isocynate in dimethyl sulfoxide and pyridine. Pullulan was substituted with 1.4 cholesterol moieties per 100 anhydrous glucoside units. The preparation was freeze dried and in aqueous phase it formed nanogel which was complexed with W-9 peptide for delivery in osteological disorders. The capacity of pullulan has been known to act as good protein carrier hence was used in nanogel formulation for drug delivery.

Further CHP has been modified with acrylate group and their thiol group was modified with polyethylene glycol by adopting Michael addition reaction, this allowed reduction in mesh size to 40 nm encapsulating 96% interleukin-12. These nanosystems have also been investigated by modifying cholesterol units by 1.1 units of cholesteryl group per 100 glucose units of parent pullulan shown significant interaction with Aβ oligomer and monomer for alzhiemer's disease treatment enhancing microglia and cortical cell viability.

More recently pullulan have been used in folate receptor targeted system in which folate was substituted to pullulan by 1.6 glucose units. Further Coupling of pullulan and photosensitizer (pheo-A) was done with carbodimide to produce the conjugate which was converted to nanogel by dialysis in DMSO against deionised water, investigated for photodynamic therapy and were successfully localized at tumor cells to cause cell death by photo destruction (Dorwal *et al.,* 2013).

Heterogeneous free radical polymerization

Various heterogeneous polymerization reactions of hydrophilic or water-soluble monomers in the presence of either difunctional or multifunctional crosslinkers have been mostly utilized to prepare well-defined synthetic microgels. They include-precipitation, inverse (mini) emulsion, inverse micro emulsion, and dispersion polymerization utilizing an uncontrolled free radical polymerization process.

Precipitation polymerization

Precipitation polymerization involves the formation of homogeneous mixture at its initial stage and the occurrence of initiation and polymerization in the homogeneous solution. As the formed polymers are not swellable but soluble in the medium, the use of crosslinker is necessary to crosslink polymer chains for the isolation of particles. As a consequence, the resulting crosslinked particles often have an irregular shape with high polydispersity.

Peppas *et al.,*synthesized narrow size distribution poly (methacrylic acid-*g*-ethylene glycol) (P (MAA-*g*-EG))nanospheres through precipitation polymerization for the oral delivery of proteins. They obtained better control over particle size and particle size distribution by controlling monomer concentration in water. They also revealed that increasing the cross-linker concentration during polymerization decreased the equilibrium swelling of the nanospheres.

Inverse (mini) emulsion polymerization

Inverse (mini) emulsion polymerization is a W/O polymerization process that contains aqueous droplets (including water-soluble monomers) stably dispersed with the aid of oil-soluble surfactants in a continuous organic medium. Stable dispersions are formed by mechanical stirring for inverse emulsion process and by sonification for inverse miniemulsion polymerization. Upon addition of radical initiators, polymerization occurs within the aqueous droplets producing colloidal particles.

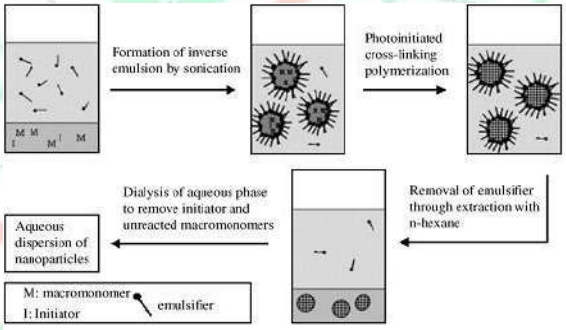


Fig. 9: Illustration of preparation for microgels of PEO-b-PPO-b-PEO via inverse emulsion polymerization.

Inverse microemulsion polymerization

While inverse (mini) emulsion polymerization forms kinetically stable macroemulsions at, below, or around the critical micellar concentration (CMC), inverse microemulsion polymerization produces thermodynamically stable microemulsions upon further addition of emulsifier above the critical threshold. This process also involves aqueous droplets, stably dispersed with the aid of a large amount of oil-soluble surfactants in a continuous organic medium; polymerization occurs within the aqueous droplets, producing stable hydrophilic and water-soluble colloidal nanoparticles having a diameter of less than 50–100nm.

Inverse microemulsion polymerization was explored for the synthesis of well-defined nanogels. Poly(vinylpyrrolidone)-based nanogels incorporated with Dex as a water-soluble macro-molecular carbohydrate drug were prepared.

Dispersion polymerization

In the process, most ingredients including monomers, polymeric stabilizers, and initiators are soluble in an organic solvent as a continuous phase.

At the onset, polymerization occurs in a homogeneous reaction mixture; however, the formed polymers become insoluble in the continuous medium, ultimately leading to the formation of stable dispersion of polymeric particles with an aid of colloidal stabilizers Hydrophilic monodisperse micron-sized particles of PHEMA were also prepared by dispersion polymerization in the presence of PEO-b-poly (1,1,2,2-tetrahydroperfluorodecyl acrylate) diblock copolymer as a stabilizer in supercritical carbon dioxide, and methacryloyl-terminated PMMA in a 55/45 (wt/wt) mixture of 2-butanol/tolune. Drugs and magnetic nanoparticles were either physically incorporated or chemically attached to microgels. The resulting microgels were effective as drug delivery carriers and for DNA applications.

MECHANISMS OF DRUG RELEASE FROM THE NANOGELS

Table 2 Mechanisms for nanogel drug release

Mechanism	Description
pH responsive	Alteration of the pH causes swelling or deswelling of the polymers that contain weakly acidic or basic groups in their structures. Amount of swelling and deswelling is governed by the extent of ionization of the polymer that in turn is determined by the pH of the medium. Hence by regulating the extent of swelling of the polymer pH governs the rate and the extent of release of the drug. e.g., Poly(*N*- vinylformamide) Nanogels releasing proteins.
Temperature Responsive	Specific polymers are tuned to impart them sensitivity for a temperature which results in the expansion of the polymeric chains and hence allowing the diffusion of the drug through.
Volume Transition	Volume transitions of nanogels feature an important application wherein nanogels increase their volume when subjected to a change in pH, temperature, light etc. This volume change triggers the drug release from the nanogel. Such a feature may also utilized for the necrotic damage of the cells as reported by (Lee et al. 2009) wherein the nanogels enter the necrotic cells as small spheres and upon imparting a cold shock the nanogels expand to high volumes that exerts a high pressure on the walls of the cell and leads necrotic cell burst. Alternatively pH change may trigger the volume expansion.
Photo responsive	In these types of nanogels, swelling and deswelling is controlled by employing photocontrollable crosslinking between the polymers. Upon incidence of the light over the nanogels their crosslinking densities alter that change their volume e.g., in case of the nanogels.

Conversion of Macroscopic Gels to Nanogels

Several synthetic methodologies are identified to prepare macroscopic gel networks (bulk gel networks or wall-to-wall cross-links) and are easy to prepare, because it is not necessary to control the synthetic parameters as are required in nanogel or microgel synthesis to control the size.The macroscopic gel networks are generally prepared by bulk polymerization, which produce a solid and the network structure with macroporous blocks.

These blocks are then crushed, grounded, and sieved to obtain gels of desired particle size. However, this is a time- and energy-consuming process and results in significant loss of material. Nevertheless, micro- and nanogels obtained from this method have particles of different shape and sizes.

APPLICATION OF NANOGELS

Following section describes in detail how nanogels are beneficial in targeting conditions related to various organs. The various conditions that the nanogels have been so far developed for are listed below and described thereafter.

A. Chemotheraphy
   i. Brain delivery
   ii. Liver delivery
   iii. Lung delivery
   iv. Skin Cancer
   v. Ovarian Cancer

B. Organ Targeting
   a. Wound healing Transdermal delivery
   b. Joint delivery
   c. Eye delivery

C. Diagnosis
   a. Imaging

D. Immunity
   a. Vaccine delivery
   b. Monoclonal antibody delivery
   c. Lupus Erythematosus

E. Anesthesia

F. Diabetes

G. Oral delivery

A. Chemotherapy

Brain delivery: A large no. of drugs are being used to treat brain disorders and other CNS related diseases but poor bioavailability of these drugs in such an organ due to poor permeability through blood brain barrier (BBB) has ever limited the entry of these drugs into the brain. Many approaches now-a-days towards brain targeting in the field of nanotechnology are leading to improved drug access to the brain but yet a more efficient nanosystem can lead us to an even better treatment of brain disorders. Polymeric nanoparticles have ever been very promising to improve drug bioavailability and some of these have great potential to cross BBB also. One of the effective nanoparticulate systems to achieve an efficient brain targeting is the use of nanogels.

Some drugs have been tried with nanogels for improvement of drug delivery to the brain. An anticancer drug, Methotrexate (MTX), is a widely used chemotherapeutic agent with a prominent position in the treatment of different cancers and autoimmune diseases and this has been formulated as nanogel. MTX was incorporated in the nanogel

Table 3 : Brain Delivery of Nanogel incorporated drugs.

Drug	Purpose of study	Approaches	Comments
N-hexylcarbamoyl-5-Fluorouracil	To increase the permeability of the drug to the brain	Coating with polysorbate 80	Increased retention in blood Increased accumulation in brain (0.52% for coated as compared to 0.1% for uncoated nanogels)
Nucleoside reverse Transcriptase inhibitors (NRTIs)	Decrease neurotoxicity and increae antiviral activity against HIV infection in the brain	Conjugated with Peptide (AP) binding brain-specific apolipoprotein E receptor	Suppression of retroviral activity by 10-fold and reduction of associated inflammation in humanized mouse model caused by HIV-1 infection in the brain
Blank Nanogels of CHP, cholesterol bearing pullulan, as artificial chaperone	Inhibit the formation of amyloid β-protein fibrils (Aβ) in Alzhiemer's Disease (AD)	Simple CHP and amino-group-modified CHP (CHPNH2) were used.	Both CHP and CHPNH2 nanogels inhibited the association of β-protein fibrils by ingesting 6-8 Aβ and hence cytotoxicity

system and surface functionalization with polysorbate was also done to improve BBB permeability.

The drug loading capacity and loading efficiency have increased largely with the use of nanogel. The *in vitro* characterization tests carried out on the prepared nanogels showed results that confirm the suitability of the nanoparticles for brain delivery target.

The study clearly showed that even with the decrease in plasma concentrations (as the drug was given as intravenous injection), the brain concentrations went increasing up to the last time point hence indicating that the drug influxed in a slow and controlled manner from plasma to brain. Both types of the nanogels (surface modified and unmodified nanogels) showed significantly higher methotrexate concentrations in the brain when compared to the free drug. The study reported an increase in the methotrexate conc. in the brain up to 10-15 folds with the use of drug-loaded nanogels, and hence offers highly prospective future to nanogels for brain delivery in future.

Vinogradov et al, developed nanogel of NRTIs (nucleoside reverse transcriptase inhibitors) for delivery to the brain for inhibition of HIV type-I in macrophages. Macrophages are regarded as reservoirs of infection that latently harbor infections like viruses and hence give them a chance to escape identification and hence treatment. This may later on lead to still major infection that would be resistant to the existing treatment. Hence in an attempt to fight latent HIV type-I viruses in macrophages, nanogel of NRTIs was formulated. The NRTIs taken were zidovudine 5'-phosphate or didanosine 5'-phosphate. The nanogel was evaluated in HIV type-I infected monocyte-derived macrophages (MDMs) for cytotoxicity, antiviral activity and intracellular accumulation. The nano-NRTIs showed high antiviral efficacy against HIV type-I in MDMs and hence established their potential for delivery to macrophages in the brain. The main advantage demonstrated with nanogels of NRTIs as against standard NRTIs was 3-fold reduction in mitochondrial toxicity caused by mitochondrial DNA depletion by NRTIs that plays main role in NRTI neurotoxicity hence reducing the chances of neurotoxicity.

For the world's most aggressive and frequent brain disorder, Human glioblastoma, Baklaushev et al., formulated cisplatin loaded nanogels conjugated with monoclonal antibodies to target the highly expressing tumor specific membrane protein known as connexin 43 (Cx43) and BSAT1 (a brain-specific anion transporter). The study reported an increased rate of survival of rats of around 27 days than the control and an increased efficiency of the formulation for the treament of gliomas.

From the above description it can be concluded that nanogel is an encouraging system for potential delivery of drugs to the CNS and has a definitive prospectus in future for the treatment of CNS disorders.

Lung delivery: Deshmukh *et al.,* prepared stabilized aggregated nanogel particles (SANP) for injectable passive lung cancer targeting by crosslinking 8 Arm PEG thiol with 1,6-Hexane-bis-vinylsulfone (HBVS) using 0.1% v/v Tween™ 80 contained in phosphate buffer (PB, pH 7.4) to incorporate prodrug of camptothecin, norvaline α-amino acid (Deshmukh et al., 2012). The formulation was developed as an alternative to the inhalation for pulmonary delivery of the drug. The anticancer efficacy of the formulated nanogels was evaluated in the lung cancer models of rats against the free camptothecin given as a bolus. The study revealed that 40% of the drug containing nanogel (0.22 mg/kg) treated animals showed 100% cancer treatment and the others also showed a significant response to the drug loaded nanogels and also to the free drug (2 mg/kg). This meant that the efficacy of the drug was increased by 10 times by incorporation in the nanogel.

Skin cancer: Melanoma is a malignant tumor of melanocytes predominantly found in skin, but can develop in any part of the body containing melanocytes. It is a potentially fatal cancer. Cutaneous melanoma comprises only 3% of all skin tumors (Sharma et al., 2009) but still about 75% of all the deaths caused by skin cancer comprise of cutaneous melanoma (Halperin et al., 2013). Methods adopted for countering the skin cancer include surgery, radiation therapy and chemotherapy. Usually a combination of surgery with either of later is preferred.

Topical formulations, for chemotherapy, in case of skin cancer have proved beneficial in imparting local action over the affected area and in increasing bioavailability of the drug. Today a lot of research is going on for including cytotoxic drugs in novel carrier systems for topical delivery as they offer a great deal

of benefits over the conventional carrier systems. In case of topical delivery of drugs the upper layer of the skin, stratum corneum, poses a barrier for the penetration of the drug (Moghadam et al., 2013).

Nanoformulations with appropriate size and surface charge provide immense platform for cytotoxic drugs to target specific sites as they possess great penetration abilities via biological membranes. Nanogels among the modern nanoformulations are becoming interesting regarding the topical delivery of drugs via these tiny gels. So far developed nanogels of skin cancer drug include chitin nanogel of 5-fluorouracil (5-FU). The study resulted in an efficient loading of about 90% of the drug in the nanogel that possessed an increased ability of swelling and drug release, at acidic pH. The nanogel was also compatible with the blood. Although the penetration of 5- FU could not improve by incorporating it in nanogel for various reasons but retention time of the gel in the deeper layers of the skin was increased up to 4-5 times. This is an advantage because melanocytes which are the targets of the therapy are present in deeper layers.

Ovarian cancer: Presently, like many other cancers, ovarian cancers are being managed by surgery followed by chemotherapy. Among various approaches that are being tried for the management of tumors, targeted delivery of the drugs is considered as revolutionary. The era of nanotechnology has diverted considerable attention towards the formulation development for targeted delivery of drugs to the tumors. Nanogels provide for the chief delivery systems that can carry large amounts of therapeutic agents to the tumors specifically. Nukolova *et al.,* have developed nanogels of different drugs (doxorubicin, cisplatin) for the treatment of ovarian cancer by using di-block polymer poly(ethylene oxide)-b-poly(methacrylic acid) (PEO-b-PMA) and conjugated with folic acid. The nanogels are designed for the tumor specific delivery of the drugs. Nanogels provide for the multiple drug carrier systems due to their extraordinary high loading capacities. Further, due to the over expression of folate receptors in ovarian tumors (and certain other human tumors also), folate conjugated nanoparticles could be directed specifically towards these tumors. The study resulted in a successful development of folate conjugated nanogels that confirmed tumor specificity through both *in vitro* as well as *in vivo* studies. The study has shown superior anti-tumor efficacy of cisplatin loaded folate nanogels with decreased renal toxicity also.

Blackburn *et al.,* have worked to develop a thermosensitive nanogel of poly(N-isopropylmethacrylamide) that contained surface localized peptides that target specifically the ovarian tumor cells. The nanogels are strongly hydrated at physiological temperature and undergo a collapsed transition at 43^{o}C. These nanogels are utilized to carry siRNA to the desired cell types or tissue that take active part in silencing of mRNA. The nanogels protect the siRNAs and help them escape endosomal uptake cell viability and toxicity studies confirmed the non-toxicity of these nanogels after their delivery. When mRNAs stop working, no proteins are synthesized and cell death follows.

B. Organ Targeting

Wound healing: When considering topical application of drugs, nanogels are among the best carriers to incorporate them in, considering their highly consistent nature and proper retention over skin (Keshavarz and Kaffashi 2013). Presently it is believed that wounds provided with a moist environment show better healing than the dry dressing and gels like nanogels offer the best option for wet dressing as the quality of recovered tissue is best in wet dressing wounds. Further the cooling effect provided by the hydrogel nanoparticles (i.e. nanogel) helps in reducing the erythema and swelling by decreasing capillary circulation at the site of application (Mallefet and Dweck). Many drugs till date have been developed in nanogel form for application over wounds.

Kobayashi *et al.,* developed cholesterol bearing pullulan (CHP) nanogel, a highly biocompatible polymer, in combination with prostaglandin (PGE1) for the treatment of wound. PGE1 has been used clinically for the treatment of wounds and chronic skin ulcers. The wound healing efficiency of the formulation was evaluated in full thickness skin defect model animals (Wistar rats).

Transdermal delivery: Permeation of the drugs via skin by transdermal delivery has improved by the use of nanogels. A similar type of nanogel was developed by for a combination of two anti-inflammatory drugs, spantide II and ketoprofen by dispersing chitosan coated PLGA nanoparticles of the drugs into HPMC or carbopol. For increasing the permeation into the skin the nanoparticles were modified by impregnating the coated nanoparticle surface with permeation enhancer, oleic acid, a monostructured fatty acid which acts to fluidize biological membranes. The oleic acid modified PLGA-chitosan bilayered nanoparticles were dispersed in a gel system (nanogel) to increase their retention time over skin and obtain controlled release drug - delivery. The nanogels were obtained with optimum particle sizes (226 nm). The gel possessed an excellent rheology being non-Newtonian and showing thixotropic behavior which is desirable for topical formulations.

In vivo studies for determining the permeation into the skin were carried out on dermatomed human skin. DNFB (2,4-dinitrofluorobenzene) induced ACD (allergic contact dermatitis), and imiquimod (IMQ) induced psoriatic plaque models were used to evaluate anti-inflammatory efficacy of the formulation in mice. The results showed that the application of the combined drug formulation improved its effectiveness in bringing down the inflammation.

Samah *et al.,* have prepared topical nanogels of Poly-(N-isopropylacrylamide-copolymerized-acrylic acid) known as [poly(NIPAM-co-AAc)] and poly(N-isopropylacrylamide) known as (polyNIPAM) incorporating the drug methotrexate for determining the mechanism by which nanogels cross the skin. The authors have used specifically prepared porcine ear membrane to evaluate the fraction of the drug crossed through the skin after the application of specific doses of polyNIPAM (control) and polyNIPAM-co-AAc nanogels. Overall control membranes were those treated by de-ionized water. The cells were disassembled after 24 hr and receptor

phases recovered and analyzed by TEM for the presence of nanogels. The TEM results confirmed the enhanced migration of polyNIPAM-co-AAc nanogels than polyNIPAM nanogels which is attributed to the dual properties i.e., response to both temperature and pH of the polyNIPAM-co-AAc nanogels compared to the mere temperature responsive property of polyNIPAM nanogels.

Singka et al., have used activated nanogels of NIPAM (copolymerized N-isopropylacryl-amide) and butylacrylate to incorporate methotrexate for improving its topical delivery and enhance anti-inflammatory action (Singka et al., 2010). Uniform sized and spherical shape nanogel particles were confirmed by TEM images. Nanogels carrying methotrexate greatly aided in increasing the drug bioavailability in the epidermis that increased the uptake by the keratinocytes and hence reducing the PGE_2 production. Permeation of the methotrexate was assessed by using heat-separated epidermal and silastic membranes.

Samah *et al.,* prepared another nanogel, pH and tempe-rature sensitive, for enhancing transdermal delivery of caffeine using poly (NIPAM-co-AAc), poly-N-isopropylacrylamide-co-acrylic acid.

Atul *et al.,*developed nanogel for transdermal delivery of aceclofenac to reduce inflammation.

Joint delivery: Macrophages are considered as keys to play role in initiation and maintenance of inflammatory disorders. Macrophages are responsible for the increased vascular and tissue permeability observed at sites of inflammation e.g., in inflamed articular joints of rheumatoid arthritis patients which suggests that their exclusive elimination may prove productive in treating inflammatory disorders. Through production of various cytokines and other chemicals during inflammation, macrophages conduct three major processes including antigen presentation, phagocytosis, and immunomo-dulation (Schmitt et al., 2010), (Fujiwara and Kobayashi 2005). And hence possess a great role to initiate, maintain, and reduce inflammation.Therefore, they may be beneficial targets of treatment aiming at their local destruction at inflammatory sites. Many studies on rheumatoid arthritis in animal models through photodynamic therapy (PDT) using the photosensitizers, photofrin, mTHPCB PDMA, or hexyl ester of 5-aminolevulinic acid have proven beneficial for PDT.

C. Diagnosis

(a) Imaging: Outlining ofa tumor is very significant in its effective removal and in that the normal tissue remains intact without any harm since visual contrast between the normal brain tissue and glioma is very poor due to their large infiltration in the normal tissues of brain. Jiang et al., have synthesized new pH/ temperature sensitive nanogels conjugated with Cy5.5-labelled lactoferrin (Cy5.5-Lf-MPNA nanogels) for imaging of glioma (a primary tumor of brain). In case of glioma, neurosurgery is presently the first line treatment. But the tumor mass is so merged with the normal tissue that it becomes very difficult to completely remove the tumor while letting no harm to the normal tissue. If the gliomas are precisely outlined it could help in their complete removal. Many techniques currently exist for imaging of tumors. The newly developed technique for the imaging of the gliomas is superior in that it offers the combined features of the existing ones.

D. Immunity

Vaccine Delivery: Vaccination is all about generation of antigen specific immune response through the use of biological agents that may be weakened or killed forms of the microbe or agents that resemble disease causing microorganisms. Development of immunogenicity includes: I) generation of antibodies and II) induction of cell-mediated immunity (i.e., stimulation of T or B cells to kill the antigen; Disis et al., 2009). For the development of immunogenicity antigens are must to enter APCs (antigen-presenting cells) to be processed internally and taken for surface presentation to T cells, to either a CD8 (cytotoxic) T-cell which directly kills the foreign cells, or to a CD4 (helper) T-cell which help cytotoxic T-cells to kill foreign cells by releasing chemical signals and also induce B lymphocytes to produce antibodies. Besides antigen presentation, T cells also require co-stimulation via the surface co-stimulatory molecules or secreted factors such as cytokines, without which T cells are not able to produce adequate response. In natural immunization, especially after infection, co-stimulation is induced by specific ligands associated with the pathogen. In case of vaccines this co-stimulation is generated by the use of adjuvants that mimic the signals usually produced by natural pathogens. Currently only a few adjuvants are approved for human use e.g., MF59, alum (aluminum salts), Montanide ISA 51, Adjuvant System 04 (AS04), Adjuvant System 03 (AS03) and virosomes (Leroux-Roels 2010), (Reed et al., 2009), (Mbow et al., 2010). A limitation of such an approach to induce immunogenicity is that these adjuvants provide immunity by merely the stimulation of antibody production and do not potentiate the cell-mediated immunity (Guy 2007). This can result in the hindrance in the prevention of diseases caused by intracellular pathogens or cancer where cellular immunity is must for the encounter (Disis et al., 2009). In order to overcome this limitation novel formulations for vaccines are being developed. Nanogels are among one of those novel delivery systems that have efficiently been able to induce long-lasting and strong immunity besides providing cell mediated immunity.

Today a large no. of vaccines based on polymeric nanogel system have been developed that include; peptide-based vaccines with the use of chitosan, PLGA, gamma PGA; protein based vaccines using mannan and pullulan, chitosan and derivatives, PLA and PLGA, PCL, PMMA etc.; DNA based vaccines using chitosan, gamma PGA, PLGA and PLA; and RNA based vaccines.

E. Anesthesia

(a) Local Anesthesia and
(b) Infiltration Anesthesia

Both types of anesthesia are referred in following paragraphs.

Duration of local anesthesia aftera surgery is a very important clinical demand. Most of the anesthetics used today possess very less duration of action. A way out of prolonging the local anesthetic release is to associate the drug with a carrier system.

With the use of nanogels it has been possible to achieve prolonged duration local anesthesia for as long as 9 hr. Using poly(N-isopropyla-crylamide), in a study, thermosensitive-nanogel of bupivacaine was developed that attained nerve block for about 9hr. 3T3 mouse fibroblasts, J.1774 macrophage-like cells, and C2C12 mouse myoblasts in cell culture were used to evaluate the cytotoxic effect of nanogel. An important observation made in the study was that higher acid functionalization of the nanogels led to slightly less cell viability than with lesser acid functionalization. Also, particle size had a little influence over the cell viability. In the end the study concluded that large nanogels with high acid functionalization led to greater cytotoxicity and increased inflammatory response. As against this, small nanogels with less acid functionalization produced lesser cytotoxic effects and very mild inflammatory response.

F. Diabetes

Researchers at the Massachusetts Institute of Technology (MIT) and Boston Children's Hospital are in progress to make a self-operating insulin delivery system using novel nanotech approach which involves single injection of a nanogel that can stabilize blood glucose level for as long as 10 days. The nanogel is glucose sensitive, detects blood-glucose levels and secretes insulin accordingly.

The MIT approach has used a nanogel containing a mixture of oppositely-charged dextran nano-particles that experience electrostatic attraction and make the gel mechanically consistent. The nanoparticles are composed of an inner core of insulin, modified dextran and glucose oxidase enzymes. As the enzyme exposes to the high glucose level in the blood it converts glucose into gluconic acid. The gluconic acid so formed disintegrates the dextran spheres and hence releases insulin which then lowers the glucose level of the blood to the normal. Being biocompatible the gluconic acid and dextran finally dissolve in the body, (Gu et al., 2013; Gu et al., 2013). Recently an optical sensitive, insulin loaded silver nanoparticle nanogel of poly(4-vinylphenylboronic acid-co-2-(dimethylamino) ethyl acrylate) [p(VPBA−DMAEA)] for the management of diabetes have been designed (Wu et al., 2010) (Fig. 6). The study conducted the introduction of the glucose sensitive p(VPBA−DMAEA) shell onto Ag NPs that made the polymer-bound Ag NPs to response against glucose.

G. Oral delivery

Kim et al., have reported interferons (IFNs) to be responsible for reduction in the replication and pathogenicity of murine norovirus (MNV) (RAW267.4 cells). where they demonstrated large reduction in the replicationof RNA and proteins due to various interferons (IFN-α, IFN-γ) and suggested them as therapeutic agents for norovirus infections, a common cause for gastroenteritis. But short half-life of IFNs due to their low stability poses a problem for their delivery to specific infection sites. Hence for a profound action of IFNs their stability was improved by incorporating them in nanogels prepared from cross linked polymers, polyethyleneimine (PEI)-polyethylenglycol (PEG) in their acetylated form (acetylated for prevention of cellular penetration & toxicity). The AcNG-acetylated nanogel and IFN-AcNg both were found to be stable in PBS solution for two weeks at room temperature as observed by AFM (Atomic Force Microscope). The study, through various assays, demonstrated AcNg to highly stabilize IFNs and also significantly increased the activity of IFNs. *In vivo* studies using rats showed no side effects by administration through systemic or oral routes. Hence it could be concluded that AcNg could serve as potential carriers for IFNs to fight norovirus infections through oral route.

CURRENT STATUS IN CLINICAL TRIALS AND FUTURE PERSPECTIVES OF NANOGELS

Nanogels have already been employed as DDS in vivo and in clinical trials, primarily for cancer therapy. In mice with subcutaneous fibrosarcoma, subcutaneous injections of recombinant murine interleukin - 12 (IL - 12) encapsulated in CHP nanogels, via incubation at room temperature, led to a prolonged elevation of IL - 12 in the sera and resulted in significant growth retardation of the tumor .Clinical trial of Cholesteryl pullulan (CHP) nanogels has shown tremendous potential in delivering peptides. The CHP-HER-2 vaccine was administered to nine patients biweekly dosing of 300μg with booster doses. The vaccine was well tolerated with some skin sensitivity at site of subcutaneous injection. All the patients showed $CD4^+$ and $CD8^+$ T-cell response suggesting better therapeutic activity (Dorwal *et al.,* 2012). CHP nanogels have further proved their prospects for clinical trails by reducing cytotoxicity of nervous system cells by showing increase in binding capacity to Aβ oligomer in treating Alzheimer's disorder.

(Lee *et al.,* 2009). Researchers (Nukolova *et al.,* 2011) have used PEO-b-PMA diblock copolymers to form nanogels with free OH groups at the PEO termini. Nanogels were then conjugated to activated folic acid with terminal amino groups, and further loaded with cisplatin or doxorubicin. On human ovarian carcinomas A2780 overexpressing folate-receptor-a, targeted nanogels would be able to specifically recognize their target. In a A2780 model subcutaneously inoculated to mice maintainedon a folate deficient diet, iv administration of the targeted nanogels would permit to enhance anti-tumor efficacy of cisplatin and to decrease the kidney toxicity compared to the free drug.This is a ongoing approach for clinical trial. Recent prospects in diabetes management by optical sensitive insulin loaded silver nanoparticle nanogel of poly(4-vinylphenylboronic acid-co-2-(dimethylamino) ethyl acrylate) have been designed opening new era in the field of clinical trial (Wu *et al.,* 2010). Development of antibiotic conjugated nanogels and their in-vivo application have given promising approach towards phase 1 clinical trail (Vinogradov, 2004). Nanogel seems to be excellent candidates for drug delivery system; more study need to be conducted at the single cell level. An investigation into the mechanisms of uptake not only at the blood – brain barrier, but also at the level of neurons and/or glial cells within the central nervous, will demonstrate which nanogels favor a cytosolic destination over an endosomal or nuclear, for example. Such studies are necessary if nanogels are ever to be proposed as

specific drug delivery systems for targeting at the subcellular level.

Conclusions

From the discussion above it is clear about nanogels that they possess a vast no. of applications regarding the targeted delivery of drugs to various organs. Nanogels exhibit the features of both the hydrogel and nanoparticles that make them a unique carrier system in that the hydrogel properties allow nanogels to accommodate a large quantity of water and hence increase their drug loading capacities, impart tissue like properties, make them flexible while nanometric size of these particles allow them to enter deeper tissues, escape invasion by reticuloendothelial system, provide site specific delivery etc. The so far research over nanogels have collected enough evidence to prove nanogels as potential targeting carriers that can deliver bioactive substances to large number of organs ranging from topical delivery of skin for conditions like skin cancer, wounds, inflammation, local anesthesia upto CNS delivery. Besides drugs, nanogels have also been further exploited to incorporate macromolecules like proteins, peptides, carbohydrates, oligonucleotides, antigens, monoclonal antibodies, genes and some inorganic molecules like quantum dots, silver nanoparticles, magnetic nanoparticles etc. Considering the above aspects of nanogels it is clear that these versatile carriers possess enough potential to offer any potential breakthrough in the treatment of diseases in future.

Nanogels are promising and innovative drug delivery system that can play a vital role by addressing the problems associated with old and modern therapeutics such as nonspecific effects and poor stability. Future design and development of effective nanogel based DDSs for in vivo applications requires a high degree of control over properties. Nanogels appear to be excellent candidates for brain delivery. One future goal of research in this area should be the improved design of microgels/nanogels with specific targeting residues to enable highly selective uptake into particular cells. This will be especially important for the targeting of cancer cells, thereby reducing non-specific uptake into healthy cells. More and more in vivo and in vitro study should be needed to confirm the use of this delivery system on human being.

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