ISSN 2249-3875

International Journal of Pharmaceutical Erudition

Review Article

A Review on Naturapolyceutics: The Science of Utilizing Natural Polymers for Drug Delivery

Nirma Paswan*, Bhupendra Vyas , Y. S. Sarangdevot, Pradeep K. Goyal
B. N. Institute of Pharmaceutical Sciences, Udaipur Rajasthan 313001

Naturapolyceutics defines the emerging science and technology platform that blends natural polymers and pharmaceutics for the design and development of drug delivery systems. Natural polymers attracts the attention of its use as they can be degraded to non-toxic monomers and most important, a constant rate of drug release can be achieved from a natural polymer based controlled release device. Natural polymers can be used as the means of achieving predetermined rates of drug delivery and their physico-chemical characteristics with the ease of availability provide a platform to use it as a polymer drug delivery systems. Natural polymers are basically polysaccharides so they are biocompatible and without any side effects. Natural polymers due to their biological properties, sustainability, chemical flexibility, human and eco-friendliness are promising in this field. As drug delivery advances, there will be need for more polymer. The versatility of natural polymers and particularly modified natural polymers in targeted drug delivery, micro-/nano-drug delivery, theranostics, BioMEMs and generally in research and development of highly efficient, safe and quality products is demonstrated. Natural polymers are polymers of today and tomorrow. Polymeric materials provide most important avenues of research. Therefore, the shift to undertake training, extensive research and subsequent commercialization of more natural polymers—novel and underutilized—for drug delivery is now! This review provides insight into the processes—modifications and characterizations—involved in the eventual utilization of natural polymers for drug delivery.

Key words: Naturapolyceutics, Biocompatible, Theranostics, BioMEMS

INTRODUCTION

Any pharmaceutical formulation contains two ingredients one is the active ingredient and other is an excipients. An excipients help in the manufacturing of dosage form and it also improves physicochemical parameters of the dosage form.

Polymers play an important role as excipients in any dosage form. A polymer is a large molecule (macromolecules) composed of repeating structural units. These subunits are typically connected by covalent chemical bonds. They influence drug release and should be compatible, non-toxic, stable, economic etc. They have wide range of applications so selection of polymer is the main step in designing any dosage form. Both synthetic and natural polymers are available but the use of natural polymers for pharmaceutical applications is attractive because they are basically polysaccharides

***Address for Correspondence**
nirmapaswan@gmail.com

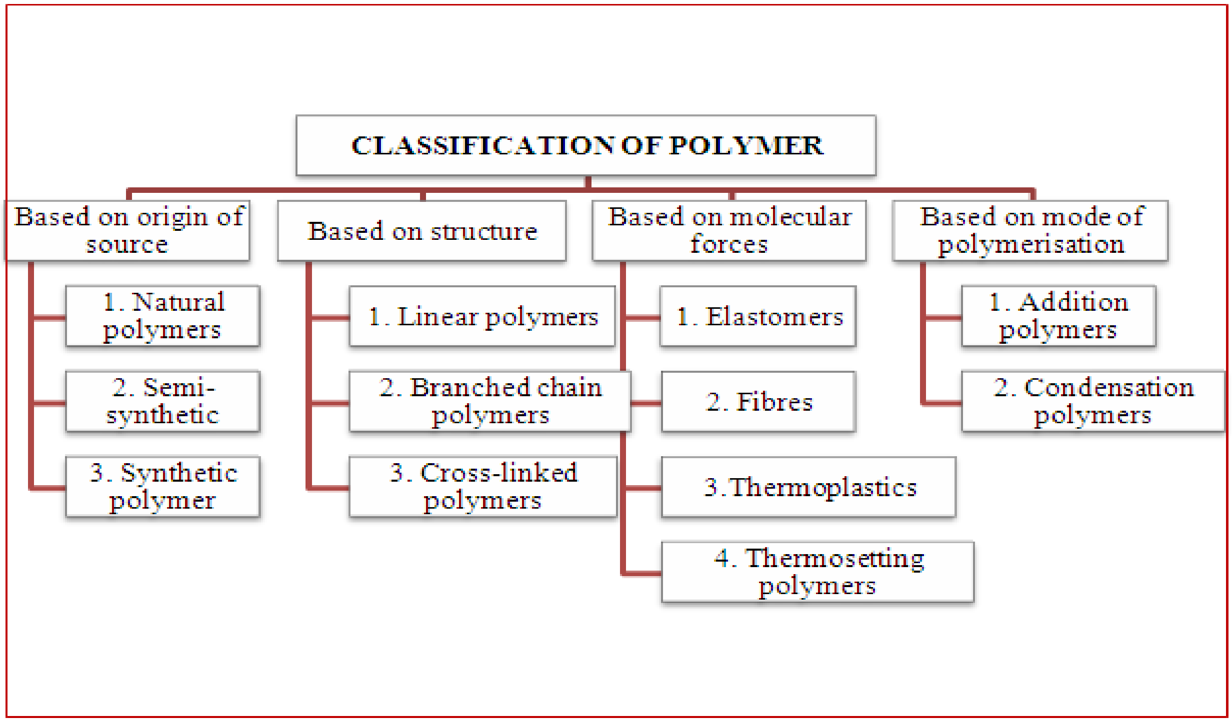

Fig.1: Classification of polymers:

so they are economical, readily available and non-toxic. They are capable of chemical modifications, potentially biodegradable and with few exceptions, also biocompatible.[1] The use of natural polymers has increased in recent times; also due to the advocacy of "green" materials from "green" chemistry and technologies. Nowadays, due to many problems associated with drug release and side effects manufacturers are inclined towards using natural polymers. Natural polymers are biogenic and their biological properties such as cell recognition and interactions, enzymatic degradability, semblance to the extracellular matrix and their chemical flexibility make them materials of choice for drug delivery. The specific application of plant-derived polymers in pharmaceutical formulations include their use in the manufacture of solid monolithic matrix systems, implants, films, beads, microparticles, nanoparticles, inhalable and injectable systems as well as viscous liquid formulations.[2-4] Within these dosage forms, polymeric materials have fulfilled different roles such as binders, matrix formers or drug release modifiers, film coating formers, thickeners or viscosity enhancers, stabilizers, disintegrants, solubilisers, emulsifiers, suspending agents, gelling agents and bioadhesives.[5]

Natural Polymers in Drug Delivery:

A system that formulates or device that delivers therapeutic agent(s) to desired body location(s) and/or provides timely release of therapeutic agent(s), such a system 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. From this, new ideas on controlling the pharmacokinetics, pharmacodynamics, non-specific toxicity, immunogenicity, biorecognition, and efficacy of drugs were generated. These new strategies, often called Drug Delivery Systems (DDS), are based on interdisciplinary approaches that combine pharmaceutics, polymer science, analytical chemistry, bioconjugate chemistry, and molecular biology.[6,7] Typical schematic examples of drug delivery systems based on polymers and nano-particulates were given in fig. 2.

Novel Drug Delivery Systems:

To deliver drugs efficiently to specific organs, a range of organic systems (e.g., micelles (fig.3) liposomes, and polymeric nanoparticles) novel ways have been designed. To minimize drug degradation and loss, to prevent harmful side-effects and to increase drug bioavailability and the fraction of the drug accumulated in the required zone, various drug delivery and drug

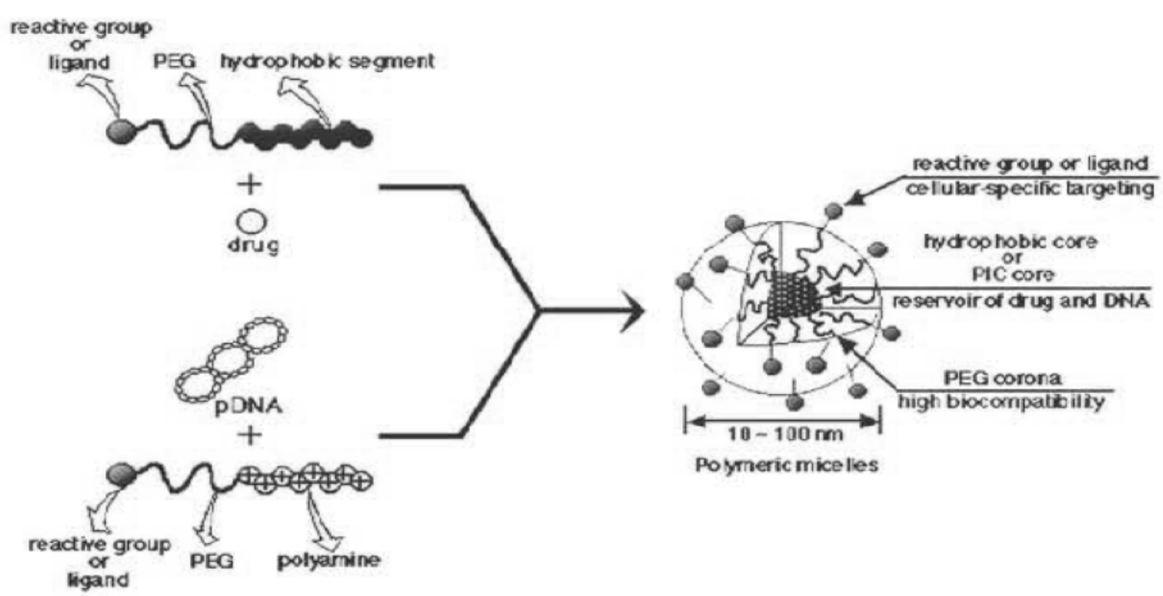

Fig. 2: Polymer Based Drug Delivery System

targeting systems are currently under research and development. Among the several drug carriers one can name soluble polymers, microparticles (fig. 3) made of

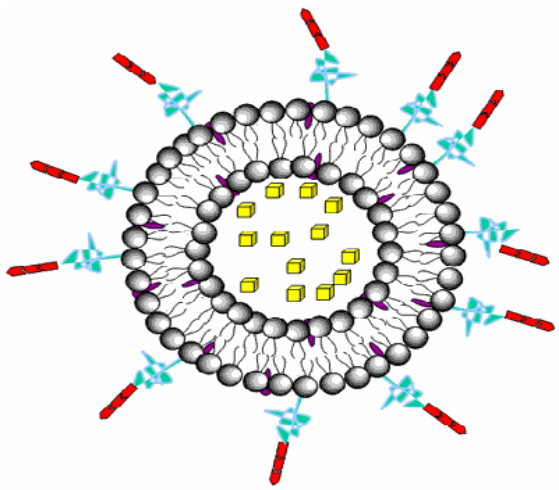

Fig. 3: Drug Carrier Micelle

insoluble or biodegradable natural and synthetic polymers, microcapsules, cells, cell ghosts, lipoproteins, liposomes, nanoparticles, Dendrimers and micelles.[8,9]

Controlled drug delivery:

Controlled drug delivery is the use of formulation components and devices to release a therapeutic agent at a predictable rate *in vivo* when administered by an injected or non-injected route. Controlled Drug Delivery (CDD) occurs when a polymer, whether natural or synthetic, is judiciously combined with a drug or other active agent in such a way that the active agent is released from the material in a predesigned manner.

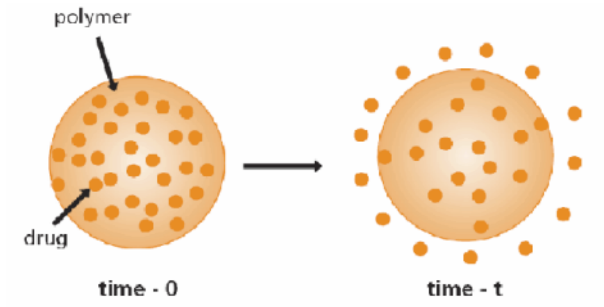

Fig. 4: Controlled Drug Delivery (CDD)

The release of the active agent may be constant over a long period, it may be cyclic over a long period, or it may be triggered by the environment or other external events. An example of Controlled drug delivery was shown in fig.4.

Natural Polymers for Controlled Release:

- *Terminalia catappa* gum-a plant exudate from *Terminalia catappa* Linn utilized in the formulation of a controlled release tablet of dextromethorphan hydrobromide, a cough suppressant.[10]
- Mucilage from fruits of *Hibiscus esculentus* controlled the release of paracetamol for over 6 h.[11]
- Natural gum/polysaccharide from plant *Hakea gibbosa* was employed as a sustained release polymer and mucoadhesive agent for buccal tablets.[12,13]

Sustained Release Drug Delivery System:

The basic rationale for sustained release drug delivery is to alter the pharmacokinetics and pharmacodynamics of drugs by using novel drug delivery systems modifying the physiological parameters. Sustained release drug delivery system not only prolongs the duration of action but also implies the predictability and reproducibility of drug release kinetics.

- **Natural polymers for intelligent drug delivery:**

Some natural polymers and their derivatives respond to certain environmental factors such as ions, pH, enzymes, temperature and electromagnetic field. Such polymers are referred to as intelligent, smart, stimuli- and environmental-responsive polymers.[14]

eg: Crosslinked *Plantago psyllium* mucilage, Crosslinked *Plantago psyllium* mucilage, Pectin, Chitosan and Hyaluronic acid.

- **Natural Polymers for Micro- and Nano Drug Carriers:**

Mucilage from the seeds of plant *Mucuna flagillepes*, Cissus gum (*Cissus pulpunea*), Khaya gum (*Khaya grandifoliola*), Irvingia gum (*Irvingia gabonensis*) and Albizia gum (*Albizia zygia* have been blended with sodium alginate to fabricate microbeads.[15]

- **Natural Polymers for BioMEMS:**

BioMEMS refers to biomedical or biological microelectromechanical systems. It is a cross-disciplinary process of utilizing and customization of microfabrication technologies for biomedical applications.

eg: Carboxymethylcellulose (CMC) and Amylopectin.

- **Natural Polymers for Theranostics:**

A theranostic refers to a delivery system fabricated to deliver both medicine and imaging agent(s) in a single dose, bridging the gap between imaging and therapy, thereby facilitating real-time monitoring of therapeutic efficacy of the incorporated drug.[16] Natural polysaccharides due to their excellent biocompatibility, low toxicity, biodegradability and functionalities that the body can identify with, make them excellent materials for theranostics.

eg: Hyaluronic acid nanoparticles (HA-NPs), Alginate, Dextran & Chitosan.[16,17]

Modification of natural polymers:

Natural polymers are modified as a means to overcome their setbacks such as drop in viscosity, microbial degradation, and partial or low solubility. In addition, modification of natural polymers enhances their drug delivery properties and versatility. Modification should be undertaken such that the natural polymers do not lose their biological properties. Methods of modification include:

- Grafting & Cross-linking
- Derivative formation
- Polymer-polymer blending

❖ Grafting & Cross-linking:

A polymer network of Psyllium husk and methacrylamide (MAAm) with ammonium persulfate (APS) was synthesized as the initiator and *N*,*N*-methylenebisacrylamide (*N*,*N*-MBAAm) as the crosslinker.[18] The synthesis was undertaken by chemically induced polymerization through free radical mechanism. The initiator, APS produced reactive sites on psyllium, methacrylamide and *N*,*N*-MBAAm. The four reactive sites on *N*,*N*-MBAAm can be linked with the radicals on psyllium and poly (MAAm) to produce a three-dimensional network, psy *cl*-poly(MAAm)—a hydrogel.

Other grafting and crosslinking with natural polymers include polyacrylamide grafted to katira gum and katira gum crosslinked with glutaraldehyde;[19,20] crosslinking of guar gum with trisodiumtrimetaphosphate[21]; cashew gum crosslinked with epichlorohydrin.[22]

❖ Formation of Derivatives:

Formation of derivatives of natural polymers are employed to enhance their physicochemical properties such as hydrophilicity, solubility, swellability, drug release, targeting, stimuli-responsiveness and film forming.[23] Such derivative formations include carboxymethylation, carbamoylethylation, cyanoethylation, acetylation, deacetylation, phosphorylation, sulfation and esterification.

- Carboxymethylation adds carboxymethyl groups to the natural polymers thereby enhancing their solubility. Natural polymers such as inulin , cashew gum , xyloglucan gum, locust bean gum , starch , hemicelluloses , konjac glucomannan , xylan, guar gum and tara gum have been carboxymethylated.
- Carbamoylethylation of mucilages and gums is undertaken with acrylamide in the presence of sodium hydroxide. Reaction parameters which influence carbamoylethylation process are the gum-liquor ratio, concentrations of sodium hydroxide and acrylamide, temperature and duration of reaction.[24]
- Cyanoethylation is another process utilized in modification of natural polymers in order to enhance their solubility and stability. The process is undertaken with acrylonitrile in the presence of sodium hydroxide. Some of the natural polymers which have been cyanoethylated include *Cassia tora* gum[25] and tamarind kernel powder.[26]

❖ Polymer-Polymer Blending:

Polymer-polymer blending is an easy and convenient approach of modifying polymers without undergoing the procedures for chemical reactions/synthesis for new polymers. The blending may be due to physical bonding whereby polymers interact by Van der Waals, hydrogen bonding and London dispersion forces. The blending may also be due to chemical bonding whereby the polymers interact by covalent bonding (crosslinking) or ionic bonding. Polymer blending is a means of improving the properties of the polymers involved. A blend of alginate, locust bean gum and xanthan gum in fabrication of microspheres enhanced drug entrapment efficiency.

Applications of natural polymers in pharmaceutical industries:

- Natural Polymers are used pharmaceutically as film-coating and microencapsulating materials to achieve sustained/controlled drug release.
- They are also used in cosmetics, chewing gums, and dental varnishes.
- Natural Polymers films may be used as rate controlling membranes for the development of transdermal drug delivery systems.
- They may be used for water-resistant coating and in pharmaceutical and dental industries.
- They are also used as a stabilizer, thickener and emulsifier extensively in pharmaceutical industry.

Advantages of natural polymers:

1. Biodegradable
2. Biocompatible and non-toxic
3. Economic
4. Safe and devoid of side effects
5. Easy availability[27]

Disadvantages of natural polymers:

1. Microbial contamination
2. Batch to batch variation
3. The Uncontrolled rate of hydration
4. Slow Process
5. Heavy metal contamination[28]

Summary & Conclusion:

Petrochemical resources are dwindling and in the near future, synthetic polymers may be in high demand thereby increasing their cost. In addition, the advocacy of green chemistry, green technology and green environment may precipitate dissatisfaction with synthetic polymers with patients insisting that the pharmaceutical industry use natural materials for the manufacture of drug delivery systems. Furthermore, utilization of natural polymers instead of synthetic polymers may reduce the cost of drug delivery systems. Natural polymers will continue to have increasing impact in drug delivery. As the shift from synthetic polymer to natural polymers continues, naturapolyceutics—extraction, purification, modifications, characterizations and applications of natural polymers in drug delivery—will continue to advance.

Polymers are the fundamental facets of drug delivery and as drug delivery technologies continue to evolve and progress, there will be increasing demands on polymers and the need for new polymers. New natural polymers are better positioned than new synthetic polymers for approval. In addition, the biological properties of natural polymers give them the edge over synthetic polymers. Natural polymers are the polymers of today and tomorrow. Therefore it behoves the polymer and pharmaceutical scientists to characterize and optimize more natural polymers, to move from bench to market.

The study and utilization of natural polymers for drug delivery (Naturapolyceutics) is imperative for the present and the future.

REFERENCES

1. Satturwar P.M., Fulzele S.V., Dorle A.K., Biodegradation and in vivo biocompatibility of rosin: A natural film-forming polymer, AAPS Pharm. Sci. Tech. 2003; 4:1-6.

2. Pandey R., Khuller G.K., Polymer based drug delivery systems for mycobacterial infections, Curr. Drug Deliv. 2004; 1: 195-201.

3. Chamarthy S.P., Pinal R., Plasticizer concentration and the performance of a diffusion-controlled polymeric drug delivery system, Colloids Surf. A. Physiochem. Eng. Asp. 2008; 331 : 25-30.

4. Alonso-Sande M., Teijeiro D., Remunan-Lopez C., Alonso M.J., Glucomannan a promising polysaccharide for biopharmaceutical purposes, Eur. J. Pharm. Biopharm. 2009; 72 (Suppl 2) : 453-62.

5. Guo J., Skinner G.W., Harcum W.W., Barnum P.E., Pharmaceutical applications of naturally occurring water-soluble polymers, PSTT. 1998; 1: 254-61.

6. Allen TM . Ligand-targeted therapeutics in anticancer therapy, Nature Rev Drug Discov 2002; 2: 750–63.

7. Harris JM, Chess RB. Effect of pegylation on pharmaceuticals, Nature Rev Drug Discov 2003; 2: 214–21.

8. Brigger I, Dubernet C, Couvreur P . Nanoparticles in cancer therapy and diagnosis, Adv Drug Del Rev 2002; 54: 631–51.

9. Muller-Goymann C.C. "Physicochemical characterization of colloidal drug delivery systems such as reverse micelles, vesicles, liquid crystals and nanoparticles for topical administration", Eu. J. of Pharm. and Biopharm., 2004; 58: 343-56.

10. Kumar, S.V.; Sasmal, D.; Pal, S.C. Rheological characterization and drug release studies of gum exudates of Terminalia Catappa Linn., AAPS

Pharm Sci Tech 2008, 9, 885–90.

11. Kalu, V.; Odeniyi, M.; Jaiyeoba, K. Matrix properties of a new plant gum in controlled drug delivery, Arch. Pharm. Res. 2007, 30, 884–89.

12. Alur, H.H.; Beal, J.D.; Pather, S.I.; Mitra, A.K.; Johnston, T.P. Evaluation of a novel, natural oligosaccharide gum as a sustained-release and mucoadhesive component of calcitonin buccal tablets, J. Pharm. Sci. 1999, 88, 1313–19.

13. Alur, H.; Pather, S.; Mitra, A.; Johnston, T. Evaluation of the gum from Hakea gibbosa as a sustained-release and mucoadhesive component in buccal tablets, Pharm. Dev. Technol. 1999, 4, 347–58.

14. Alvarez-Lorenzo, C.; Blanco-Fernandez, B.; Puga, A.M.; Concheiro, A. Crosslinked ionic polysaccharides for stimuli-sensitive drug delivery, Adv. Drug Deliv. Rev. 2013, 65, 1148–71.

15. Odeku, O.A.; Okunlola, A.; Lamprecht, A. Microbead design for sustained drug release using four natural gums, Int. J. Biol. Macromol. 2013, 58, 113–20.

16. Wang, Z.; Niu, G.; Chen, X. Polymeric materials for theranostic applications, Pharm. Res. 2013, 1–19.

17. Park, S.Y.; Baik, H.J.; Oh, Y.T.; Oh, K.T.; Youn, Y.S.; Lee, E.S. A smart polysaccharide/drug conjugate for photodynamic therapy, Angew. Chem. Int. Ed. 2011, 50, 1644–47.

18. Singh, B.; Chauhan, N. Modification of psyllium polysaccharides for use in oral insulin delivery, Food Hydrocoll. 2009, 23, 928–35.

19. Bharaniraja, B.; Jayaram Kumar, K.; Prasad, C.M.; Sen, A.K. Different approaches of katira gum formulations for colon targeting, Int. J. Biol. Macromol. 2011, 49, 305–10.

20. Bharaniraja, B.; Jayaram Kumar, K.; Prasad, C.M.; Sen, A.K. Modified katira gum for colon targeted drug delivery, J. Appl. Polym. Sci. 2011, 119, 2644–51.

21. Gliko-Kabir, I.; Yagen, B.; Penhasi, A.; Rubinstein, A. Phosphated crosslinked guar for colon-specific drug delivery: I. Preparation and physicochemical characterization, J. Control. Release 2000, 63, 121–27.

22. Silva, D.A.; Feitosa, J.P.A.; Maciel, J.S.; Paula, H.C.B.; de Paula, R.C.M. Characterization of crosslinked cashew gum derivatives, Carbohydr. Polym. 2006, 66, 16–26.

23. Prajapati, V.D.; Jani, G.K.; Moradiya, N.G.; Randeria, N.P. Pharmaceutical applications of various natural gums, mucilages and their modified forms, Carbohydr. Polym. 2013, 92, 1685–99.

24. Gupta, S.; Sharma, P.; Soni, P.L. Chemical modification of Cassia occidentalis seed gum: Carbamoyl-ethylation, Carbohydr. Polym. 2005, 59, 501–6.

25. Sharma, B.R.; Kumar, V.; Soni, P.L. Cyanoethylation of Cassia tora gum, Starch Stärke 2003, 55, 38–42.

26. Goyal, P.; Kumar, V.; Sharma, P. Cyanoethylation of tamarind kernel powder, Starch Stärke 2008, 60, 41–7.

27. Girish K. Jani, Dhiren P. Shah, Vipul D. Prajapati, Vineet C. Jain, Gums and mucilages: versatile excipients for pharmaceutical formulations Asian J. Pharm. Sci. 2009; 4 (Suppl 5) : 309-32.

28. Shirwaikar A., Prabu S.L., Kumar G.A., Herbal excipients in novel drug delivery systems, Indian J. Pharm. Sci. 2008; 70 : 415-22.