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REVIEW ARTICLE

RECENT TRENDS OF NOVEL DRUG DELIVERY IN TREATMENT OF DIABETIS MELLITUS

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ABSTRACT

D*iabetes mellitus is a metabolic disorder, characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both. The effects of diabetes mellitus include long-term damage, dysfunction and failure of various organs. Although the availability of new agents for treatment of diabetes mellitus, oral hypoglycemic are base of therapy, because they are relatively economical and well tolerated. A well designed controlled drug delivery system can overcome some of the inconvenience of conventional therapy and enhance the therapeutic efficacy of a given drug. This review article discusses the potential applications of novel drug delivery systems (NDDS) for diabetes treatment. NDDS includes microspheres, nanoparticles, niosomes, proniosomes etc., which are preferably used in treatment of this disease. There are a few limitations in the use of conventionally available drug delivery systems. Lack of target specificity, altered effects and diminished potency due to drug metabolism in the body, cytotoxicity of certain anti- carcinogenic pharmacological agents, are to mention a few. Biocompatible nanoparticles with optimized physical, chemical and biological properties can overcome these limitations and serve as effective drug delivery systems. These newer generations of drug delivery systems have significant advantages over conventionally available drug delivery systems.*

Key words: *novel drug delivery systems, diabetes mellitus, Insulin.*

INTRODUCTION

Diabetes (Diabetes mellitus) is classed as a metabolism disorder. Metabolism refers to the way our bodies use digested food for energy and growth, what we eat is broken down into glucose. Glucose is a form of sugar in the blood and it is the principal source of fuel for human body. When food is digested the glucose makes its way into bloodstream, our cells use the glucose for energy and growth. However, glucose cannot enter our cells without insulin being present; insulin makes it possible for our cells to take in the glucose. Insulin is a hormone that is produced by the pancreas. After eating, the pancreas automatically releases an adequate quantity of insulin to move the glucose present in our blood into the cells, and lowers the blood sugar level.

A person with diabetes has a condition in which the quantity of glucose in the blood is too elevated (hyperglycemia). This is because the body, does not produce enough insulin, produces no insulin, or has cells that do not respond properly to the insulin the pancreas produces. This results in too much glucose building up in the blood. This excess blood glucose eventually passes out of the body in urine. So, even though the blood has plenty of glucose, the cells are not getting it for their essential energy and growth requirements. It is characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both. The effects of diabetes mellitus include long-term damage, dysfunction and failure of various organs. Diabetes mellitus may present with characteristic symptoms such as thirst, polyuria, blurring of vision, and weight loss. In its most severe forms, ketoacidosis or a non- ketotic hyperosmolar state may develop and lead to stupor, coma and, in absence of effective treatment,death. The long-term effects of diabetes mellitus include progressive development of the specific complications of retinopathy. People with diabetes are at increased risk of cardiovascular, peripheral vascular and cerebrovascular disease. [1-3]

Type -1

Type 1 indicates the processes of beta–cell destruction that may ultimately lead to diabetes mellitus in which “insulin is required for survival” to prevent the development of ketoacidosis, coma and death. Type 1 is usually characterized by the presence of anti–GAD, islet cell or insulin antibodies which identify the autoimmune processes that lead to beta–cell destruction.

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Type -2

Type 2 is the most common form of diabetes and is characterized by disorders of insulin action and insulin secretion, either of which may be the predominant feature. Both are usually present at the time that this form of diabetes is clinically manifest. By definition, the specific reasons for the development of these abnormalities are not yet known.

Other specific types

Other specific types are currently less common causes of diabetes mellitus, but are those in which the underlying defect or disease process can be identified in a relatively specific manner. They include, for example, fibrocalculous pancreatopathy, a form of diabetes which was formerly classified as one type of malnutrition–related diabetes mellitus. [1 2 3]

Treatment strategies for management diabetes mellitus

1. Type 1 diabetes is invariably treated with insulin.
2. Type 2 diabetes is often allied with obesity. Serum insulin levels are normal or elevated, so this is a disease of insulin resistance. Type 2 is frequently treated by oral hypoglycemic.

Novel drug delivery system for management of Diabetes Mellitus[5]

Novel drug delivery system is a new approach to drug delivery. It helps the drug to act longer and more effectively. This overcomes limitations of old methods of drug administration. In novel drug delivery technology; control of the distribution of drug is achieved by incorporating the drug in carrier system or in changing the structure of the drug at molecular level. Microspheres, niosomes, proniosomes, micro emulsions, etc each and every formulation has its own importance in specifying its activity.

Drawbacks of conventional dosage forms[6]

1. Poor patient compliance, increased chances of missing the dose of a drug with short half life for which frequent administration is necessary.
2. The unavoidable fluctuations of drug concentration may lead to under medication or over medication.
3. A typical peak-valley plasma concentration time profile is obtained which make attainment of steady-state condition difficult.
4. The fluctuations in drug levels may lead to precipitation of adverse effects especially of a drug with small therapeutic index whenever over medication occur.

Advantages of novel drug delivery systems

1. Enhancement of solubility.
2. Increased bioavailability.
3. Protection from toxicity.
4. Enhancement of pharmacological activity.
5. Enhancement of stability.
6. Improved tissue macrophages distribution.
7. Sustained delivery.
8. Protection from physical and chemical degradation.

Novel drug delivery system for management of Diabetes Mellitus[7]

1. Microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers, which are biodegradable in nature and ideally having a particle size less than 200μm. This is the important approach in delivering therapeutic substance to the target site in sustained and controlled release fashion.

Advantages of microspheres

- Increase bioavailability
- Alter the drug release & separation of reactive core from other materials.
- Improve the patient's compliance
- Reliable means to deliver the drug to the target site with specificity, if modified, and to maintain the desired concentration at the site of interest without untoward effects.
- Reduce the reactivity of the core in relation to the outside environment.
- The size, surface charge and surface hydrophilicity of microspheres have been found to be important in determining the fate of particles in vivo.
- Decrease evaporation rate of the volatile core material.
- Convert liquid to solid form & to mask the bitter taste.
- Protects the GIT from irritant effects of the drug.
- Biodegradable microspheres have the advantage over large polymer implants in that they do not require surgical procedures for implantation and removal.
- Controlled release delivery biodegradable microspheres are used to control drug release rates thereby decreasing toxic side effects, and eliminating the inconvenience of repeated injections.

Limitations

- Removal once injected is difficult.
- Sometimes non-uniformity of drug content may result while preparation.
- Unknown toxicity of beads.

Review on various oral hypoglycemic microspheres.

Drug	Polymer	Method used for preparation	Advantages
Glipizide	Sodium alginate	An orifice-ionic gelation process	1. significant hypoglycemic effect.
	Carbopol 971		
	Chitosan	Simple emulsification phase separation technique	1.increase absorption, improve drug efficiency and decrease dose requirements.
Metformin Hydrochloride	Ethyl cellulose	Non-aqueous Solvent evaporation Method	1. maximum prolonged drug release at gastrointestinal Ph. 2. improve the bioavailability of the drug as well as patient compliance.
	Sodium carboxy methyl cellulose		
	carbopol		
	Hydroxyl propyl methyl cellulose k4m (hpmc)	Emulsification solvent evaporation	
	Eudragit rs100		
Repaglinide	Chitosan	Solvent evaporation method	1. reduce dosing frequency and improve patient compliance.
	Eudragit rs-100		
Rosiglitazone	Sodium carboxy methylcellulose	Emulsification Solvent evaporation method	1. reduce the dosing frequency and improve patient compliance 2. sustained delivery.
	Carbopol 934		
Pioglitazone Hcl	Sodium alginate	Orifice ionic gelation method	1. once a day medication. 2. good entrapment efficiency. 3. improved bioavailability.
	Carbopol 934		
	Carbopol 931		
	Carbopol 974		
	Polycarbophi		
	HPMC K100 M		

Proniosomes are recent development in Novel drug delivery system. These are most advanced drug carrier in vesicular system which overcomes demerits of liposomes and niosomes. These, hydrated by agitation in hot water for a short period of time, offer a versatile vesicle delivery.

Advantages of proniosomes [10-18]

- improvement in bioavailability and permeation of the drug .
- ease of manufacture and scale up .
- reduction in drug toxicity because of their non-ionic nature of the surfactant .
- more physical and chemical stability as compared to niosomes ,liposomes.
- osmotically stable .
- used for targeted drug delivery of drugs .
- They are used for sustained as well as controlled drug delivery system .

Limitations

- Complex process During hydration to niosomes,
- the complete drug entrapment may not be possible, some times Hence the amount of the un entrapped drug should be analyzed.

Review on Proniosomal drugs used in treatment of Diabetes mellitus

Drug	Polymer	Method used for preparation	Advantages
Gliclazide loaded maltodextrin based proniosomes	Span 60,maltodextrin	Slurry method	1. gliclazide as once a day therapy for diabetic patients. 2. better oral bioavailability. 3. high penetration property & stability of gliclazide niosomes.
Metformin proniosomal gel	Span 60,span 40	Co-aservation phase seperation method	1.enhance the bioavailability of MH by oral route.
	Span 20,span 40,tween 80,tween40	Slurry Method	1. effective sustain the release of dru& High entrapment efficiency.

Few niosomes formulations'

Drug	Polymer	Method used for preparation	Advantages
Metformin	Span 40,dicetyl phosphate	Reverse phase evaporation technique	1.enhanced the bioavailability by oral route & sustained release
	Span 20,span 40,tween 80,tween40	Ether injection method.	1.ensure a good oral bioavailability
Niosome loaded Insulin	Brij 52,brij 92,span 60	Film hydration hydration technique	1. to protect this protein against proteolyticenzymes and to improve its oral bioavailability.
Gliclazide	Span 60	Liquid film hydration technique	1. improved bioavailability and prolonged drug release profile.
Repaglinide	Span 60	Lipid film hydration	1. proved to be a good substitution for the oral form in the market. 2. uniform controlled release action.

Nanoparticles [19-16]

- Nanoparticles are defined as particulate dispersions or solid particles with a size in the range of 10-1000nm.
- The drug is dissolved, entrapped, encapsulated or attached to a nanoparticle matrix.
- Depending upon the method of preparation, nanoparticles, nanospheres or nanocapsules can be obtained.
- Nanoparticles (NPs) can be used as a multiparticulate delivery system to obtain prolonged or controlled drug delivery.

Advantages

- Particle size and surface characteristics of nanoparticles can be easily manipulated to achieve both passive and active drug targeting after parenteral administration.
- Controlled release and particle degradation characteristics can be readily modulated by the choice of matrix constituents.
- Drug loading is relatively high and drugs can be incorporated into the systems without any chemical reaction; this is an important factor for preserving the drug activity.
- Site-specific targeting can be achieved by attaching targeting ligands to surface of particles or use of magnetic guidance.
- limitation of fluctuations within the therapeutic range.
- a reduction in side-effects,
- decreased dosing frequency
- and improved patient compliance

Limitations

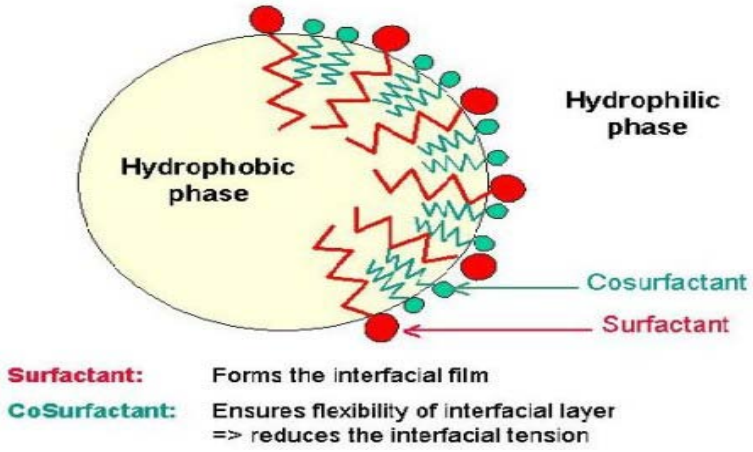
- Their small size and large surface area can lead to particle-particle aggregation.
- making physical handling of nanoparticles difficult in liquid and dry forms.
- In addition, small particles size and large surface area readily result in limited drug loading and burst release.

Review on Nanoparticles used in treatment of Diabetes mellitus

Drug	Emulsifier & lipids	Method used for preparation	Advantages
Metformin hydrochloride	Polymethacrylic acid soya lecithin	Solvent diffusion technique	1.enhanced bioavailability. 2.safe, painless and cost effective drug delivery system for diabetes patients.
Repaglinide(RPG)	Tween80 ,cephalin,lecithin	Hot homogenization technique	1.colloidal size range, a good loading capacity and drug release.
	Tristearin,poloxmer188	Micro emulsion method	1.prolonged release for oral delivery and to improve bioavailability of RPG
Oral insulin	Poloxamer 407, cetyl palmitate	W/O/W double emulsion techinque	1. protect insulin against chemical degradation in the gastrointestinal tract and to promote the intestinal absorption of insulin. 2. development of an optimized oral insulin formulation.
Oral Insulin	Poly lactic co glycolic acid(PLGA)	Modified multiple emulsion solvent evaporation	1.improved hypoglycemic effect for oral insulin delivery. 2.can decrease rapidly the blood glucose level .
	Chitosan+alginate	Ionotropic pre-gelation method	1.improvement of its oral absorption and oral bioactivity
	PLGA+sodium oleate +polyvinyl alcohol	hydrophobic ion pairing (HIP) method	1.improve the apparent liposolubility of insulin.
	Stearic acid+soybean phospholipids+poloxamer 188	spontaneous emulsion solvent diffusion method	1. relatively improved pharmacological bioavailability.
	Dextran-vitamin B12 (3%)	emulsion method	1. to deliver orally effective insulin.
glibenclamide	Eudragit L 100	Solvent displacement technique	1.enhanced effi-cacy, to reduce dose frequency, decrease side effects, and improve patient compliance.

Microemulsions

"**Microemulsions** are liquid dispersions of water and oil that are made homogenous, transparent (or translucent) and thermodynamically stable by the addition of relatively large amounts of a surfactant and a co-surfactant and having diameter of the droplets in the range of 100 – 1000 A (10 – 100 nm)."



Advantages of Microemulsion Based Systems

1. Microemulsions are thermodynamically stable system and the stability allows self-emulsification of the system whose properties are not dependent on the process followed.
2. Microemulsions act as supersolvents of drug.They can solubilize hydrophilic and lipophilic drugs including drugs that are relatively insoluble in both aqueous and hydrophobic solvents. This is due to existence of microdomains of different polarity within the same single-phase solution.
3. The dispersed phase, lipophilic or hydrophilic (oil-in-water, O/W, or water-in-oil, W/O microemulsions) can behave as a potential reservoir of lipophilic or hydrophilic drugs, respectively.The drug partitions between dispersed and continuous phase, and when the system comes into contact with a semi-permeable membrane, the drug can be transported through the barrier. Drug release with pseudo-zero-order kinetics can be obtained, depending on the volume of the dispersed phase, the partition of the drug and the transport rate of the drug.
4. The mean diameter of droplets in microemulsions is below 0.22 mm; they can be sterilized by filtration. The small size of droplet in microemulsions e.g. below 100 nm, yields very large interfacial area, from which the drug can quickly be released into external phase when absorption (in vitro or in vivo) takes place, maintaining the concentration in the external phase close to initial levels.
5. Same microemulsions can carry both lipophilic and hydrophilic drugs.
6. Because of thermodynamic stability, microemulsions are easy to prepare and require no significant energy contribution during preparation. Microemulsions have low viscosity compared to other emulsions.
7. The use of microemulsion as delivery systems can improve the efficacy of a drug, allowing the total dose to be reduced and thus minimizing side effects.
8. The formation of microemulsion is reversible. They may become unstable at low or high temperature but when the temperature returns to the stability range, the microemulsion reforms.

Disadvantages Of Microemulsion Based Systems

1. Use of a large concentration of surfactant and co-surfactant necessary for stabilizing the nanodroplets.
2. Limited solubilizing capacity for high-melting substances
3. The surfactant must be nontoxic for using pharmaceutical applications
4. Microemulsion stability is influenced by environmental parameters such as temperature and pH. These parameters change upon microemulsion delivery to patients.

Review on Micro emulsion formulations used in treatment of Diabetes mellitus

Drug	Surfactant & co-surfactant	**Method used for preparation**	**Advantages**
Glipizide	Transcutol,cremophor	Water titration method	1. improving the bioavailability of poor water soluble compounds. 2. enhance the dissolution rate and bioavailability .
Insulin	Tween 80,iso propyl alcohol	Conventional titration method	1. enhanced permeation and bioavailability.

Recent Advances in Insulin Delivery System

Insulin Pens: Insulin pen injectors are a convenient and discreet way of administering insulin. They have a built-in dial that allows you to determine the amount of insulin to be injected, a short needle at one end and a plunger at the other. Some are disposable and don't need to be assembled before use, while others have a replaceable insulin cartridge that needs to be inserted (much like a fountain pen cartridge).

- Insulin pens are particularly useful if you need to take premixed insulin. They have become popular for use by people with both type 1 and type 2 diabetes.

Insulin Jet Injectors: Jet injectors offer an alternative to needles and work by sending a fine spray of insulin into the skin using a pressurized jet of air instead of a needle.

External Insulin Pumps: External insulin pumps are small devices the size of a pager that can be attached to your belt or placed in your pocket. They run off batteries. They are made up of an insulin reservoir connected to a tube, ending in a cannula or catheter, which is inserted under the skin of your abdomen. They can be set to deliver insulin at a slow, continuous rate throughout the day, or to release larger quantities at meal times or when blood sugar levels are high. The main advantage of a pump is that it closely mimics the slow but continual release of insulin by the pancreas. but the risk of episodes of low blood sugar (hypoglycaemia) is higher. Another drawback of pumps is the risk of ketoacidosis if the catheter becomes blocked. Expense may also be an issue.

Implantable Pumps: Implantable pumps which deliver insulin either intravenously or directly to the liver are currently being tested in people with diabetes (they are not yet available in Australia). They are usually implanted into the left side of the abdomen and are designed to work in a similar way to external insulin pumps, that is, by giving a continuous 'basal' dose of insulin with the ability to deliver additional 'bolus' doses at meal times. Also under investigation is a version of the pump that measures blood glucose as well and so delivers the correct insulin dose automatically. However, these devices are complicated and expensive and can become blocked. If there are complications or infection at the implantation site the pump may have to be removed.

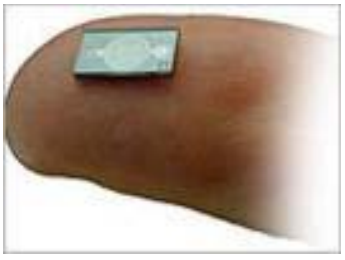
Insulin Patches: Insulin patches are also currently under development, but it is difficult for insulin to be absorbed through the skin. The patch is designed to release insulin slowly and continuously. Additional doses can be administered by pulling off a tab on the patch.

Insulin Inhalers: Insulin inhalers are a new way of delivering pre-mealtime insulin. Insulin inhalers work like an asthma inhaler, but deliver dry powdered insulin into the bloodstream via the lungs. However, because the system can only be used to deliver fast-acting insulin, long-acting insulin must still be injected. Large doses are needed because only around 10 per cent of the dose actually reaches the bloodstream and that amount may vary, for instance, if you have a cold or asthma. The inhalers are not yet commercially available in Australia, but have been approved for use in the USA.

Future Trends for Insulin Delivery Systems: Insulin sprays, either for the nose or mouth and oral insulin (insulin pills) are methods of insulin delivery that continue to be investigated. These options represent long-term possibilities for insulin delivery, as difficulties in obtaining adequate amounts of insulin in the bloodstream are yet to be overcome.

Islet Cell Transplantation: This is a recently developed surgical procedure - called the Edmonton protocol - whereby islet cells from a donated human pancreas are injected into the liver of a recipient with type 1 diabetes. The transplanted cells begin to secrete insulin, while the recipient needs to take immunosuppressive medications for life to prevent rejection of the transplanted tissue. Clinical trials continue to establish the safety and long- term effectiveness of this procedure as a means of supplying insulin.

Insulin Nanopump: The nanopump is a powerful device and has many possible applications in the medical field. The first application of the pump, introduced by Debiotech, is Insulin delivery. The pump injects Insulin to the patient's body in a constant rate, balancing the amount of sugars in his or her blood. The pump can also administer small drug doses over a long period of time.



Gene Therapy: Two recent reports describe research into gene therapy for different aspects of diabetes. These reports are in the forefront of what will no doubt be ongoing and exciting research arising from the decoding of the human genome.

- Scientists have identified a gene called SHIP2 that appears to regulate insulin. Such findings make SHIP2 a potential gene therapy target for the treatment of type 2 diabetes aimed at improving the individual insulin regulation.
- A protein that blocks the overgrowth of blood vessels in the eye is being studied as possible gene therapy for diabetic retinopathy. A recent study showed that treatment with the protein, called pigment epithelium-derived factor, or PEDF, prevented excessive new blood vessel formation in an animal model of retinopathy. It may also be used to treat macular degeneration.
- As scientists identify specific genes whose absence or improper functioning are associated with specific conditions, more possibilities for gene therapy are offered for diabetes as well as all disease.

CONCLUSION

The forgoing review shows different aspects related with the novel drug delivery system (NDDS)approaching a vital role to deliver a drug by different route to achieve better therapeutic action.Inspite of certain drawbacks, NDDS still play an important role in the selective targeting and controlled delivery of various drugs. Researcher are implementing their efforts in improving the design of NDDS by making them steady in nature,inorder to prevent leaching of contents, oxidation and their uptake by natural defense mechanism. As their flexibility in design posses a wide range of potential, its application must be explored throughout the world by encouraging the participation of researcher in the field of Novel drug delivery system.

REFERENCES

1. *www.staff.ncl.ac.uk/philip.home/who_dmc.htm*
2. KARTHIKEYAN SUBRAMANI, SARVADAMAN PATHAK, HOSSEIN HOSSEINKHANI RECENT TRENDS IN DIABETES TREATMENT USING NANOTECHNOLOGY.
3. http://www.medicinenet.com/script/main/a…
4. B. Rathore, A. Yadav, G. Nayak, G. K. Saraogi and A. K. Singhai INTERNATIONAL JOURNAL OF PHARMACY & LIFE SCIENCES A review on microspheres as drug delivery carriers for management of diabetes mellitus.
5. Recent Trends in Novel Drug Delivery System. - Pharmainfo.net b**y** Aruna Rastogi *www.pharmainfo.net/reviews/recent-trends-novel-**drug-delivery**-system*
6. Jain SK, Awasthi AM, Jain NK, Agrawal GP, J Control Release, 2005; 107; 300-309.
7. Vyas and Khar Targeted and Controlled drug delivery (CBS Publishers and distributors,2001).
8. Prasanth V, Moy A, Mathew S, Mathapan R "Microspheres - An Overview" IJRPBS, Jun 2011 332-338.
9. Alagusundaram M, Madhu Sudana Chetty C, Umashankari K, Badarinath AV, Lavanya C and Ramkanth S "Microspheres As a Novel Drug Delivery System : A Review" IJCTR. 2009, 1, 526-534.
10. Sandeep Loona, Nitan Bharti Gupta, M.U.Khan PREPARATION AND CHARACTERIZATION OF METFORMIN PRONIOSOMAL GEL FOR TREATMENT OF DIABETES MELLITUS Int. J. Pharm. Sci. Rev. Res., 15(2), 2012; no 21, 108-114.
11. Azza A. HasanHafez Madkor, and Sherief Wageh http://informahealthcare.com/doi/abs/10.3109/10717544.2013.779332
12. D. Akhilesh, V. N. Anoop, Dr. B.P. Rao Formulation and Evaluation of Gliclazide Loaded Maltodextrin Based Proniosomes Vol. 2(4) Oct - Dec 2011.
13. S Tamizharasi, A Dubey, V Rathi, JC Rathi Development and characterization of niosomal drug delivery of gliclazide journal of young pharmacists **Year** : 2009,**Volume** : 1,**Issue** : 3, **Page** : 205-209.
14. M. Madhavi, C. P. Meher, B. Pochaiah, A. M. Rao1 Formulation and evaluation of metformin based niosomes International Journal of Pharma Research & Review, Jan 2013; 2(1):1-7.
15. El-Feky S. Gina, Abu-Elyazid K. Sherif 1, Abd Allah I. Fathy 2 Asian J. Pharm. Hea. Sci. | Oct-Dec 2012 | Vol-2 | Issue-4.
16. Mahmoud mokhtar Ahmed Ibrahim, Omamia A. sammour, Mohamed A. Hammad and Nagia A. megrab, "In vitro Evaluation of proniosomes as a drug carrier", AAPS PharmSciTech, vol. 9, no. 3, September 2008, pg no. 782 – 789
17. Almira I. Blazek- Welsh and David G. Rhodes, " SEM imaging of malto dextrin based proniosomes" , Journal of pharmaceutical research, vol. 18, no. 5, February 12 th , 2001, plenum publishing corporation, pg no. 656 -661.
18. Walve J.R., Rane B.R. , Gujarathi N.A, BakaliawalS.r, PanwarS.p, "proniosomes: A surrogated carrier for improved transdermal drug delivery" , International Journal of Research in Ayurveda and Pharmacy, vol. 2, no.3, 2011, pg no. 743 – 750.
19. Akhilesh.D, Fishal.G, Kamath.JV, " Comparitive Study of Carriers Used In Proniosomes", International Journal Of Pharmaceutical And Chemical Sciences, vol. I, Jan-Mar 2012, pg no: 164-173.
20. VJ Mohanraj and Y Chen2 Nanoparticles – A Review Tropical Journal of Pharmaceutical Research, June 2006; 5 (1): 561-573.

21. Gourav Joshi, Seema Saini, Sandeep Arora1, Arvind Sharma, Vikas Kumar INNOVATION IN GASTRORETENTIVE DRUG DELIVERY SYSTEMS: FORMULATIONS AND TECHNIQUES FOR ANTI-DIABETIC DRUGS IJAPR / April 2011/ Vol. 2 / Issue. 4 /147- 156.
22. Bruno Sarmento, Susana Martins, Domingos Ferreira, and Eliana B Souto Oral insulin delivery by means of solid lipid nanoparticles Int J Nanomedicine. 2007 December; 2(4): 743–749.
23. .Navneet Sharma Transdermal patches based on solid lipid nanoparticles of metformin: Novel approach for drug delivery of type 2 Diabetes www.omicsgroup.com/conferences/biomolecularengg2013/
24. Jameel Ahmed S. Mulla, Shivanandswamy P. Hiremath, Naveen Kumar Sharma Repaglinide Loaded Solid Lipid Nanoparticles: Design and Characterization RGUHS J Pharm Sci | Vol 2 | Issue 4 | Oct–Dec, 2012.
25. V.Vijayan, D.Srinivasa Rao1. E.Jayachandran, J.Anburaj Preparation and characterization of Anti Diabetic Drug Loaded Solid lipid Nanoparticles V.Vijayan1 et al. /JITPS 2010, Vol.1 (8), 320-328.
26. CHANDER PARKASH DORA, SHAILENDRA KUMAR SINGH, SANJEEV KUMAR, ASHOK KUMAR DATUSALIA and AAKASH DEEP DEVELOPMENT AND CHARACTERIZATION OF NANOPARTICLES OF GLIBENCLAMIDE BY SOLVENT DISPLACEMENT METHOD Acta Poloniae Pharmaceutica ñ Drug Research, Vol. 67 No. 3 pp. 283Ñ290, 2010.
27. Zhi Min Wu1, Li Ling1, Li Ying Zhou, Xin Dong Guo, Wei Jiang, Yu Qian, Kathy Qian Luo and Li Juan Zhang Novel preparation of PLGA/HP55 nanoparticles for oral insulin delivery Wu et al. Nanoscale Research Letters 2012, 7:299.
28. Sarmento B, Ribeiro A, Veiga F, Sampaio P, Neufeld R, Ferreira D. Alginate/chitosan nanoparticles are effective for oral insulin delivery. Pharm Res 24: 2198-2206, 2007c.
29. Cui F-D, Tao A-J, Cun D-M, Zhang L-Q, Shi K. Preparation of insulin loaded PLGA-HP55 nanoparticles for oral delivery. J Pharm Sci 96: 421-427, 2007.
30. Zhang Z, Lv H, Zhou J. Novel solid lipid nanoparticles as carriers for oral administration of insulin. Pharmazie 64(9):574-578, 2009.
31. Chalasani KB, Russell-Jones GJ, Yandrapu SK, Diwan PV, Jain SK. A novel vitamin B(12)-nanosphere conjugate carrier system for peroral delivery of insulin. J Control Release 117: 421-429, 2007a.
32. Shaji, J., Reddy, M.S.; Microemulsions as drug delivery systems, Pharma Times, 2004, 36 (7); 17.
33. Razdan, R., Devarajan, P.V.; Microemulsions, Indian Drugs, 2003, 40 (3); 139 – 146.
34. Schott, H.; Colloidal Dispersion In Remington: The science and practice of pharmacy, Twentieth Edition; Ed: Gennaro, A.F.; Lippincott Williams and Wilkins, 2000, Vol-1; 313 – 314.
35. Nairn, J.G.; Solutions, emulsions, suspensions and extracts in Remington: The Science and Practice of Pharmacy, Twentieth Edition; Ed: Gennaro, A.F.; Lippincott Williams and Wilkins, 2000, Vol-1; 740 – 741.
36. Hoar, T.P., Schulman, J.H.; Transparent water-in-oil dispersions: the oleopathic hydro-micelle, Nature, 1943, 152; 102–103.
37. Schulman, J.H., Stoeckenius, W., Prince, L.M.; Mechanism of formation and structure of micro emulsions by electron microscopy, J. Phys. Chem.,1959, 63; 1677–1680.
38. Shinoda, K., Friberg, S.; Microemulsions- Colloidal aspects, Adv. Colloid Interface Sci.,1975, 4; 281–300.
39. Deshpande, S.G., Bajaj, A., Sawarkar, S.P.; Intraarterial and intravascular drug delivery systems In Advances in Controlled and Novel Drug Delivery; Ed: Jain, N.K.; CBS Publishers and Distributors, New Delhi, 2001; 182 – 183.
40. Vyas, S.P., Khar, R.K.; Submicron emulsions in targeted and controlled drug delivery, Novel Carrier Systems; CBS Publishers and Distributors, New Delhi, 2002; 282 – 302.
41. Biresh K Sarkar* Shiv S. Hardenia Microemulsion Drug Delivery System: For Oral Bioavailability Enhancement of Glipizideournal of Advanced Pharmacy Education & Research 1(4): 195-200 (2011) ISSN 2249-3379.
42. Jadupati Malakar, Suma Oomen Sen, Amit Kumar Nayak, and Kalyan Kumar Sen Development and Evaluation of Microemulsions for Transdermal Delivery of Insulin ISRN Pharm. 2011; 2011: 780150.
43. Al-Tabakha, M.M. and A.I. Arida, 2008. Recent challenges in insulin delivery systems: A review.Indian J. Pharm. Sci., 70: 278-86.
44. Insulin Delivery Systems Market Analysis, 2007- 2010. information available form: www.marketresearch. com, access date: 23/01/2009.
45. Korytkowski, M., D. Bell, C. Jacobsen, *et al*. 2003. FlexPen Study Team. A multicenter, randomized,open-label, comparative, two-period crossover trial of preference, efficacy and safety profiles of a prefilled,disposable pen and conventional vial/syringe for insulin injection in patients with type 1 or 2 diabetes mellitus. Clin. Ther., 25: 2836-2848.
46. Advances in Diabetes, Information Available form: www. lifeclinic.com, access Date: 23/01/2009.

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