Pak. Jour. of Pharm. Sciences
Vol. 10, No.2, July, 1997, pp.41-50

CURRENT PERSPECTIVES AND OPPORTUNITIES FOR INTERNATIONAL COOPERATION FOR DEVELOPMENT OF POLYMER BASED DRUG DELIVERY SYSTEMS

NEVINE A. ABDULLAH* AND MOHAMED H. SOROUR**
**Department of Pharmaceutical Sciences*
***Department of Chemical Engineering and Pilot Plant*
National Research Centre, Dokki, Cario, Egypt

ABSTRACT

The present paper is devoted to:
Analysis of significant endeavours directed to polymer base drug delivery systems, elucidating addressing priority problems and biopolvner development, significant R&D needs and priorities and the framework as well as the requirements for international networking in the area of dreg delivery system.

Such organized collaboration will enable promotion of knowledge among interested parties and cultures.

Concerned pharmaceutical institutional and scientific associations e.g. International Pharmaceutical Federation FIP and American Association of Pharmaceutical Sciences AAPS should adopt and initiate planned activities for developing and activation of appropriate drug network encompassing active members from the academic, professional centres and drug industry.

The proposed network should be established on a self-sustained basis.

Polymers used in Drug Delivery System, DDS:

Recent advances pertinent to DDS incorporate different types of polymers within the matrix of the DDS to protect the active ingredients and to induce slow release characteristics.

Table 1 depicts different examples based on R/D trials for the use of polymer within the matrix of Insulin delivery system.

In spite of the limited success achieved so far, it is expected that commercial cost effective systems will be developed within few years.

Numerous polymers are also present within the DDS for specific applications including amiprotornal agents, analgesics and antipyretics, antidepressive agents... etc. The polymer mix may employ sugar grafted liposomes, hydrogels, collagen/chitosan, cyclodextrin... etc., c.f table 2.

Problems Encountered with DDS (uncertainty areas)

1. Technical Problems:

The most significant technical problems are related to the following:

a) Polymer/enhancer drug interaction.
b) Pharmacokinetics of dissociation.
c) Driving force for inclusion complexation (cyclodextrin enhancers). Etiology and profiles of toxicity related to the polymers/enhancers.
d) Impact of drug delivers systems on drug pharmacokinetics.
e) Chemical stability of the polymer and the drug.
f) Monitoring of delayed release pattern.
g) Biocompatibility of implantable drug delivers systems.
h) Enzymatic inhibition of oral peptide absorption.
i) Reliability and quality control requirements.

2. Institutional-Type Problems, ITPs

ITPs that should be resolved especially in the third world are

a) Lack of information exchange among R&D institutions. Medical and Industrial Community.
b) Inadequate networking on the regional and international levels.
c) Issues related to intellectual property right.
d) Regularity requirement and constraints.

3. Financial Problems:

Financial problems include

a) Insufficient funding for R&D within the Academia.
b) Need for high capital to implement high tech. systems.

R and D Needs and Priorities

a) Basic Issues

Basic issues for future R & D endeavours should focus on polymer biodegradability, stability, toxicity, bioavailability and long term monitoring.

b) Specific Issues

Specific R & D *issues* includes, but not limited to the following.

- Comparative evaluation of safety requirements for different drug delivery systems and administration mutes.
- Development of appropriate in-vitro simulation techniques for drug absorption distribution, excretion and metabolism for different administration mutes.
- Quantitative evaluation of bioavailability for the drug/polymer mix.
- Comparative toxicological and availability evaluation for the employed polymer and its derivatives.
- Development of specific absorption enhancers.
- Quantitative risk assessment of developed enhancers on target absorption sites.
- Development of appropriate oral peptide delivery systems manifesting program release of the peptide and the inhibitor of the protolytic activity.
- Improving colonic drug targeting mechanisms.
- Quantitative evaluation of polymer degradation and impacts.
- Synthesis, testing and evaluation of advanced specific lwdrogel based drug delivery systems.

The role of international cooperation

The development of suitable DDS is mandatory for extending the service boundaries of the drug industry and also to overcome observed problems manifested by current DDS. International cooperation should enable exchange of ideas, concepts, information, resources and scientists. Effective international networking is an appropriate mechanism to realize this objective. Thus an international network served by regional centres could be initiated through the collaborative efforts of scientific institutes and associations, professional centres and drug industry. For instance, FIP and AAPS can coordinate the efforts to start such a network. The basic ideas and concepts of this network are presented in Figs.1, 2 and 3.

In essence, the activities of the DDS should include. but not limited to linkage with R&D Centres, Industry Medical Centres in addition to human resources development and initiation of expert group meetings.

The concepts of this network if properly vitalized would lead to considerable support for pharmaceutical institutions in developing countries.

Table 1

	Insulin Delivery	Route	Main Findings	Ref.
1.	Matrix system including insulin, absorbance gelatin sponge (insulin eye drop)	Ocular	• Substantial improvement: in insulin bio-availability. • Significant duration of the pharmacological response. • More gradual blood glucose reduction	1
2.	Microemulsions	Oral	Several microemulsion formulations were demonstrated to be promising for oral delivery of insulin	3
3.	Insulin-sodium salicylate in a medium viscosity hydroxypropyl cellulose vehicle	Oral	Significant glucose lowering activity in rabbits	3
4.	Insulin 5 kinds of cyclodextrin in phosphate buffer solution at pH=7	Nasal	• Marked increase in the plasma level of the insulin. • Marked decrease in glucose content ratio. • Recovery of the membrane transport function.	4
5.	Insulin with five kinds of cyclodextrin	Nasal	Enhancement of insulin diffusivity across nasal membrane through dissociation may provide an additional mechanism for cyclodextrin promotion of nasal insulin absorption.	5

	Insulin Delivery	Route	Main Findings	Ref.
6.	The insulin was administrated with 0.5% saponin, 0.5% and 1% BL- 9, 0.5% and 1% dodecylmaltose, and 0.5 and 1% tetradecylmaltoside	Eye drops	This study demonstrated that short-acting insulin is systemically absorbed in dogs via the ocular route when applied with certain emulsion. Significant changes in serum glucose.	6
7.	Effect of enhancers e.g. bile salts (cholate, glycocholate, taurocholate and deoxycholate) and nonionic surfactants	Trans-dermal	They increased the number of charged insulin and thus increased the solubility of Insulin. This formulation delivered insulin very effectively through the skin and reduced blood glucose level by 60% for 10 hours.	7
8.	Insulin with bioadhesive polymers: 1.5% w/v microcrystalline cellulose (MCC) and 70% w/w plastid L 50 alone or with Ammonium glycyrhizinate (AG) or Glycyrrhetinic acid (GA)	Nasal	The bioavailability of insulin increased • The glucose values was reduced.	8
9.	Insulin plus 0.06-0.25% tetradecylmaltose or dodecylsucrose and nonylglycoside	Nasal	The alkylglycosides appear to represent a promising new family of peptide drug absorption-enhancing agent. The use of insulin nasal drops in rats provides a convenient model of peptide drug absorption	9

	Insulin Delivery	Route	Main Findings	Ref.
10.	Liposome mixed with insulin solution. Three kinds of liposomes neutral positively and negatively charged liposome-insulin.	Pulmonary	A stronger response was observed with the positively charged liposome (DPPC): Chol: stearylamine = 7:2: 0.5) these results indicate that factors such as lipid species, concentration and charge play important roles in liposome-facilitated pulmonary insulin absorption.	10
11.	Human insulin with specific ligands such as zinc, phenol and m- cresol	Subcutaneous injection	These techniques illustrate that insulin analogs that are both stable and fast acting can be achieved through formation of stable associated states with altered dissociation properties.	11
12.	Microemulsion: Polyglycerol fatty acid ester / cosurfactant / captex 300 / water	Oral	Several microemulsion formulations were demonstrated to be promising for oral delivery based on the results of stability tests and acid-protection efficiency.	12

Table 2
Polymer in Drug Delivery Systems

Ser.	Drug	Route	Polymer/ Enhancer	Impact Potential clinical significance	Ref.
1.	Pentamidine isethionate and its methoxy der. (Antiprotozoal agents)	Oral (Mannose grafted liposomes)	Sugar grafted liposomes	+ve	13
2.	Cyclosporine A	Ocular	Poly-epsilone caprolactone	+ve	14
3.	Ketanserin hydrogels	Wound side	Ultrapure poly (vinyl alcohol)	++ve	15
4.	5-Fluororuacil	Subcutaneously implanted	Copolymeric poly (acrylamide-co-monopropyl itaconate	Promising	16
5.	Dexamethasone	Intraluminal infusion	Biodegradable polyactic-polyglycolic acid copolymer	++ve	17
6.	Nifedipine	Transdermal in-vitro	Collagen/chitosan membranes	Promising	18
7.	Proxyphyline (herbicide)	In-vitro	Poly (ethylene) oxide) xerogel	Promising	19
8.	Proxyphylline	Potential oral delivery	Ultrapure cross-linked poly (ethylene oxide)	Promising	20

Ser.	Drug	Route	Polymer/ Enhancer	Impact Potential clinical significance	Ref.
9.	Biphenyl acetic acid (Anti-inflam-matroy)	Oral	Beta-cyclodextrin Ester type conjugate)	Promising	21
10.	Benzodiazepines (Antidepressive agents)	Oral	Hydroxypropyl methylcellulose/ lactose	Promising	22
11.	Acetaminophen (Analgesic and antipyretic)	Oral (in-vivo) and in-vitro	Gelation of hydrophillic matrices containing polythylene oxide	Promising	23

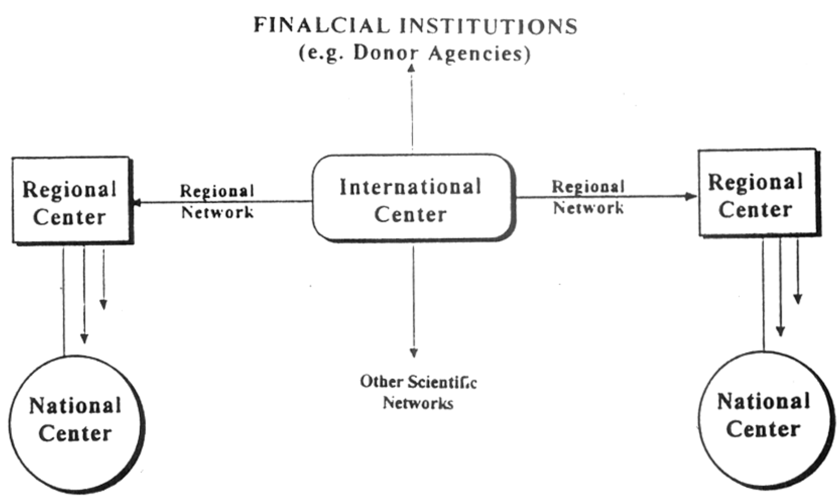

Fig. 1: Proposed international Network for Drug Delivery Systems DDS.Net.

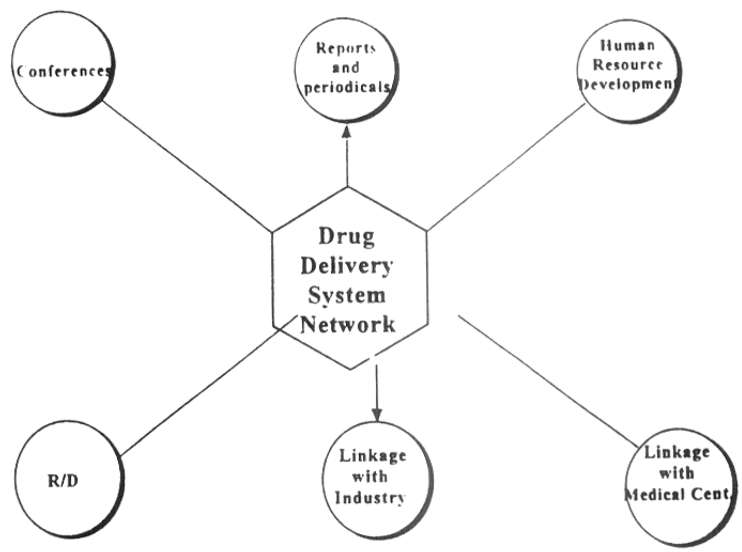

Fig. 2: Principal Activities of the Drug Delivery System Network.

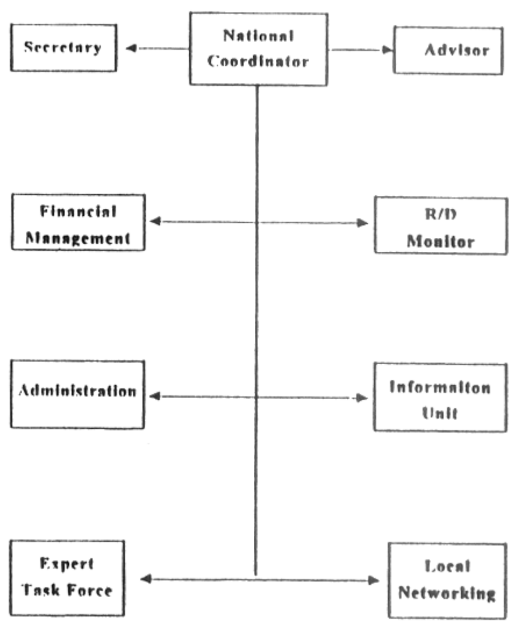

Fig. 3: Proposed Structure of Local Drug Delivery System Network.

REFERENCES

Bakaysa D.L., Beals J.M., Brader M.L., Dodol S.W., Edwards S.L., Havel H.A., Radziuk J. and Brems D.N. (1994). *Pharm. Res.* **11**(10): 7404.

Banerjee G., Nandi G., Mahato S.B., Pakrashi A. and Basu M.K. (1996). *J. Antimicrob. Chemother.* **38**(1): 145.

Blanco M.D., Garcia O., Olmo R., Teijon J.M. and Katime I. (1996). *J. Chromatogr. B. Biomed. Appl.* **680**(1-2): 243.

Brown T.R. and Smith M.C. (1996). In: "Institutional Pharmacy Practice". Ed. Williams and Wilkins. 2nd Edition.

Calvo P., Sanchez A., Martinez J., Lopez M.I., Calonge M., Pastor J.C. and Alonso M.J. (1996). *Pharm. Res* **13**(2): 311.

Dondeti P., Zia H. and Needam T .E. *Pharm. Res.* **11**(10): 7124.

Gao P., Skoug J.W., Nixon P.R.. Ju T.R., Stemm N.L. and Sung K.C. (1996). *J. Pharm. Sci.* **85**(7): 732.

Guzman L.A., Labhasetwar V., Song C., Jang Y., Lincoff A.M., Levy R. and Topol E.J. (1996). *Circulation.* **96**(6): 1441.

Hirayame F., Minami K. and Uekame K. (1996). *J. Pharm. Pharmacol.* **48**(1): 27.

Ho H., Hsiao C.C. (1996). *J. Pharm. Sci.* **85**(2): 138.

Ho H.O., Hsiao C.C. and Sheu M.T. (1996). *J. Pharm Sci.* **85**: 138.

Li Y. and Mitra A.K. (1994). *Pharm. Res.* **11**(10): 7151.

McNeill M.E. and Graham N.B. (1996). *J. Biomater. Sci. Polym.* Ed. **7**(11): 953.

McNeill M.E. and Graham N.B. (1996). *J. Biomater. Sci. Polym,* Ed. **7**(11): 937.

Mesiha M. and Sidhom M. (1995). *Int. J. Pharm.* **114**: 137.

Mongia N.K., Anseth K.S. and Peppas N.A. (1996). *J. Biomater Sci. Polym.* Ed. **7**(12): 1055.

Morgan R.V. and Huntzieker M.A. (1996). *J Ocul. Pharmacol. Ther.* **12**(4): 515.

Pillion D.J. and Meezan E. (1994). *Pharm. Res.* **11**(10): 7127.

Sako K., Nakashina H., Sawada T. and Fukui M. (1996). *Pharm. Res.* **13**(4): 594.

Shao Z., Krishnamoorthy R. and Mitra A.K. (1992). *Pharm. Res.* **9**: 1157.

Shin B.C. and Lee H.B. (1995). *Pharm. Res.* **12**(9): 7332.

Simamora P., Lee Y.C. and Yalkowsky S.H. (1996). *Pharm. Sci.* **13**: 7271.

Thacharodi D. and Rao K.P. (1996). *Biomterials.* **17**(13): 1307.

Watanabe Y., Matsumoto Y., Kawamoto K., Yazawa S. and Matsumoto M. (1992). *Chem. Pharm. Bull.* Tokyo **40**(11): 3100.