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Mini Review Articles

DRUG DELIVERY ENHANCEMENT STRATEGIES THROUGH CORNEA: A REVIEW

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ABSTRACT

Eye is the specialized organ for photoreception that poses unique challenges for drug delivery. Eye diseases can be treated with systemic, intraocular and/or topical administration of drugs. The review highlights the challenges in ocular drug delivery through various routes with emphasis on topical route. The corneal transport process for different drugs is also touched. Different approaches for drug delivery enhancement through cornea are discussed with special attention on chemical modification (prodrug) approach. Nutrient transporter targeted prodrug design approach are discussed with special reference to amino acid prodrug design approach for enhanced drug delivery.

INTRODUCTION

Eye and Ocular Disorders

Eye is a specialized organ for photoreception. Various diseases (e.g. Conjunctivitis, endophthalmitis, retinitis, glaucoma, uveatis, cataract) can adversely affect this delicate and sensitive organ. Different categories of drugs are available in ocular therapeutics to treat these clinical conditions. Medication is applied to the surface of the eye (topically) for two purposes: to treat outside of the infections as conjunctivitis, keratitis, blepheritis or to provide intraocular treatment through the cornea for diseases such as glaucoma or uveitis[1].

Challenges In Ocular Drug Delivery

Ocular diseases may be treated by systemic, intraocular or topical administration of drugs. Eye poses unique challenge by virtue of blood aqueous and blood retinal barriers present in eye that limits the access of drugs to the eye when given through systemic route. Moreover, higher dose of a drug is required systemically for effective treatment of ocular ailments though this route as compared to intraocular and topical route which further may elicit its side effects.[2] Intraocular (injection and implants) route is associated with patient complaint problems. In most of the cases a surgery is required to explore this route of drug delivery. [3,4,5]

To treat disorders and diseases of eye, drugs given by topical route may get access to various ocular tissues. Drugs are administered topically in variety of dosage forms. Among those eye drops are perhaps the most popular dosage forms and revealed by the fact that these constitutes nearly 90% of the accessible marketed ocular formulations[6]. Despite of popularity in ophthalmology a major problem associated with topical eye drop instillation is the attainment of an optimal drug concentration at the site of action. After instillation of an eye drop, typically less than 5 % of the applied drug penetrates the cornea and reaches to intraocular tissues. Poor bioavailability of drugs from eye drops is mainly due to the precorneal loss factors which include tear dynamics, non-productive absorption, transient residence time in the cul-de-sac, and the relative impermeability of the corneal epithelial that limit their accessibility into the eye where site of action is located for most of the ocular drugs. Nevertheless, the practical reasons for selecting eye drops as a mean of drug delivery are the generally favorable cost advantage, the greater simplicity of formulation development and production and the most important is greater acceptance by patient [7-11].

Transport of Drugs Through Cornea

The cornea is considered a major route of ocular penetration for topically applied drugs. Anatomically, cornea is composed of three main layers epithelium, stroma, and endothelium. The outer- most layer, the corneal epithelium, is the major rate limiting barrier for drug

absorption, because it is a protective barrier that limits the access of foreign sub- stances into the eye[12, 13]. Usually, the lipophilic corneal epithelium, which is 6-7 cell layers thick (50-90 μm), is the main barriers of drug absorption (particularly for hydrophilic drugs) into eye. Intercellular tight junctions (Zonula occludence) completely surround the most superficial corneal epithelial cells. Drug penetration across cornea occurs via transcellular and paracellular pathways[14]. For most of the ocularly applied drugs, passive diffusion is thought to be the main transport process across cornea. Physicochemical properties of drug, such as lipophilicity, solubility, molecular size and shape, drug charge, and degree of ionization affect the transport pathways and transport rate of drug across the tissue [15-19]. Trends in drug discovery sector indicate that out of every 9000-10000 drug molecules identified as potential candidate, only 1 on average reaches to market. The reason lies behind is lacking of optimal physicochemical properties that are necessary for any drug candidate to cross biological barriers (cornea) efficiently in order to elicit the desired therapeutic response[20]. Lipophilic drugs prefer the transcellular pathway and follows classical pH partition hypothesis. Hydrophilic molecules penetrate through cornea following paracellular pathway that involves passive or altered diffusion or carrier mediated transport. The barrier properties of cornea arise from high electrical resistance of both the outermost cell membranes and paracellular zonula occludence that renders delivery of hydrophilic compounds to the deeper corneal layers a major challenge in ocular therapeutics [21-23].

DRUG DELIVERY ENHANCEMENT APPROACHES THROUGH CORNEA

1. Improvement of Ocular Retention Time

Various systems have been designed during the past two decades to maximize ocular drug absorption. The traditional methods of improving ocular penetration are those, which increase the ocular contact time of the drug (viscosity imparting agents for mechanical obstruction of drainage, formulating ointments) [24-27]. These approaches succeed to a very little extent and were associated with patient related problems (blurred vision).

2. Permeation Enhancer Approach

Another approach included the use of penetration enhancers that modifies the epithelium properties and integrity. Studies revealed that penetration enhancers (like EDTA, surfactants, quaternary ammonium compounds) while promoting corneal permeation of drugs might also damage the cornea [28-38].

3. Chemical Modification (Prodrug) Approach

(a) Conventional Prodrug Design

By changing drug's permeation characteristics (prodrug approach) ocular availability of poorly absorbed drugs may be enhanced. In last three decades a lot of research has been carried out for increasing permeability of poorly absorbed drugs across cornea by means of increasing lipophilicity through ester prodrug design. Increasing lipophilicity to a certain degree lower epithelial resistance by increasing the partitioning of drug in epithelial cell layers. However only limited success has been achieved by this approach because continued increase in lipophilicity lowers permeation across cornea. In addition increased lipophilicity of modified drug candidate possessed poor aqueous solubility and hence present problems in formulation into eye drops [39-52].

(b) Transporter Targeted Prodrug Design

Mammalian cells express different type of transport systems to transport hydrophilic molecules (nutrients) across lipid bilayers of epithelial cells, which are required to maintain integrity of cell functions. These include peptide, nucleosides, monocarboxylic acid, bile acid, ascorbic acid, folic acid, organic acid, phosphate, glucose and amino acid transporters [53-61].

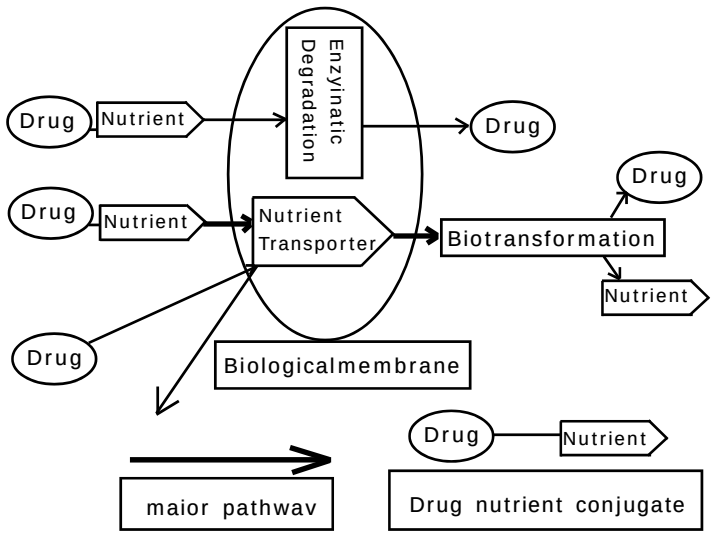

Figure 1: Concept of Nutrient Transporter Targeted Drug Delivery Through Biological Membrane

The identified transporters may be explored to increase drug permeability through biological membranes by mean of prodrug design approach. This may be achieved by chemical conjugation of a parent drug with the specific substrate in such a manner that the conjugate may be transported by the carrier system across the cell membrane. Specific nutrient transporter proteins located on various body membranes would recognize the nutrient and drug conjugate that results in translocation of the conjugate across the membrane. Subsequent biotransformation of prodrug/conjugate would split in drug and nutrient. Prodrugs/conjugates designed to resemble various nutrients structurally, are expected to be absorbed via specific carrier. This strategy of aiming the membrane transporters holds tremendous potential for enhanced drug delivery through biological barriers (Figure 1).

1. Amino Acid Transporters Targeted Prodrugs

In mammalian cells multiple systems operate to mediate the transport of amino acids, and these transport systems differ markedly in their substrate specificity, substrate affinity, sodium dependence and pH dependence. Numerous amino acid transport systems have been characterized at the molecular level including L, y^+L, A, ASC, asc, $b^{0,+}$, B0,+ and x^-, Gly, N, and T [62-68]. Various ocular tissues like conjunctiva, retinal-pigmented epithelium, are known to have presence of some of these transporters. Limited information is available on the presence of amino acid transporters on corneal epithelium. Existence of oligopeptide transporter has been reported in rabbit corneal epithelium[69]. A Na^+ dependent cationic and neutral amino acid transporter $B^{0,+}$ has been identified recently in human and rabbit corneas[70].

To explore the feasibility of improvement of ocular bioavailability of the antiviral agent acyclovir by designing amino acid prodrugs targeted to the amino acid transporters on the rabbit cornea Mitra et al studied the transcorneal flux of two water soluble ester prodrugs drugs of acyclovir glutamate and L-tyrosine. They reported that design of amino acid prodrugs seems to be an attractive strategy to enhance the solubility of the otherwise poorly aqueous soluble compounds and also to afford a targeted and possibly enhanced delivery of the active drug.[71] The same research group evaluated a series of dipeptide monoester ganciclovir (GCV) prodrugs with the goal of improving ocular bioavailability of GCV from topical ophthalmic solutions. They demonstrated that dipeptide ester prodrugs of ganiciclovir (with amino acid, valine) showed excellent corneal permeability and chemical stability, high aqueous solubility, and substantial in vivo antiviral activity against the HSV-1 [72].

2. Peptide Transporter Targeted Prodrugs: There are several reports of successful use of peptide transporters for improving drug delivery. PepT1 system transports Di and tripeptides but not free amino acids or peptide with more than 3 amino acid residues. PepT2, another peptide transporter that is responsible for transport of small peptides. Designing of peptidomimetic prodrugs of ceftibutan, fosinopril, antiviral compounds (acyclovir, ganciclovir and valacyclovir) and beta lactam antibiotics with PepT1 and PepT2 substrates have shown improved drug delivery [73,74].

3. Nucleoside Transporters Targeted Prodrugs: In mammalian cells, transcellular flux of nucleoside and nucleobases has shown to be mediated specific nucleoside and nucleobase transporters. An example of nucleoside transporter′s role in drug delivery is the movement of the anti-HIV drug 2′,3′-dideoxyinosine across blood-brain barrier [75].

4. Monocarboxylic Acid transporters Targeted Prodrugs: The Monocarboxylic acid transporters expressed by retinal pigmented epithelial cells may be targeted by monocarboxylate prodrugs for enhanced uptake (eg. Ganciclovir, acyclovir).[76]

5. Folate Transporters Targeted Prodrugs: This receptor may be explored for targeted drug delivery of anticancer drugs (folate receptor is upregulated in cancer cells).[77]

6. Others: In the similar manner mentioned above prodrug design targeting to ascorbic acid, bile acid, vitamin B12, transferrin receptors may explore new avenue for improved drug delivery.

CONCLUSION

Drug delivery across cellular barriers, such as intestinal, nasal, buccal, alveolar, vaginal, ocular and blood-brain, is a challenging task. Many factors such as cellular organization, efflux, and chemical and enzymatic degradation, as well as physicochemical properties of

the drug molecule itself, determine the penetration of drugs across epithelial cell layers. Limited intestinal absorption of many novel and highly potent lead compounds has stimulated an intense search for strategies that can effectively enhance permeation across these biological barriers. Several approaches have been tried to overcome membrane permeability problems for poorly absorbed drugs. Prodrugs targeted towards membrane transporters expressed on epithelial cells are perhaps the most exciting of all the current drug delivery strategies This approach achieved success in drug delivery enhancement through various epithelial barriers. Membrane transporter targeted drug delivery utilizing the nutrients linked compounds however is relatively unexplored particularly in case of ocular therapeutics. So far not many people have considered utilizing carrier mediated transport mechanisms on cornea, which is believed as major route of absorption for topically applied drugs. Prodrug design with water-soluble nutrient offers dual advantages. For example, on one hand prodrug design with amino acids that targets amino acid transporters will increase the corneal permeability thereby will provide increased accessibility of poorly absorbed drugs to interior ocular tissues while on other hand eliminating eye drop formulation problem (water soluble prodrugs) as compared to conventional prodrugs that are intended to enhance lipophilicity. Limited information is available about existence of amino acid transporters on cornea. More studies on amino acid transport systems will certainly help in understanding the mechanisms of corneal transport and identification of various transport systems that could be targeted for enhanced drug delivery via prodrug design approach. The transporters thus identified may be explored for improved delivery of drugs from various categories like NSAIDs, antiglaucoma, antivirals etc. Moreover in future, proteomics is going to rule the drug therapy and more studies on transport of amino acids and analogues through cornea may open new avenues for improved topical ocular drug delivery of drugs.

REFERENCES

1. Sayako E. Moroi, Paul R. Litcher. Ocular Pharmacology. IN: Goodman and Gilman's-The Pharmacological Basis of Therapeutics. Hardman J. G, Limbird L.E. (EDS.). New York: MC. Graw-Hill, 2001; 1819-1848.

2. Robinson, J.C. Ocular Anatomy and Physiology Relevant To Ocular Drug Delivery. In, Ophthalmic Drug Delivery Systems. (Mita. A.K. ED.) Marcel Dekker, New York. 1993, pp. 29-58.

3. Behar CF. Drug delivery to target the posterior segment of the eye. Med Sci (Paris). 2004; (6-7): 701-6

4. Marvin E. Myles, Donna M. Neumann, James M. Hill. Recent progress in ocular drug delivery for posterior segment disease: emphasis on transscleral iontophoresis. Advanced drug delivery reviews 57 (2005) 2063– 2079

5. Gholam A. Peyman, Gary J. Ganiban. Delivery systems for intraocular routes. Advanced drug delivery reviews 16 (1995) 107-123

6. Fitzgerald, P., Wilson Cg. Polymeric systems for ophthalmic drug delivery, in: polymeric biomaterials (S. Dimitriu, ed.), Marshel Dekker, New York, 1994, pp. 373-398.

7. Lang JC. Ocular drug delivery conventional ocular formulations. Adv drug delivery rev. 1995, 16; 39-43.

8. Lee V H L. Precorneal, corneal and postcorneal factors. In, ophthalmic drug delivery systems. (Mita. A.K. Ed.) Marcel Dekker, New York. 1993, pp. 59-82.

9. Shell, J.W., Baker, R., 1974. Diffusional systems for controlled release of drugs to the eye. Ann. Ophthalmol. 6, 1037– 1043.

10. Le Bourlais, C.L., Acar, L., Zia, H., Sado, P.A., Needham, T., Leverge, R., 1998. Ophthalmic drug delivery systems—recent advances. Prog. Retin. Eye res. 17, 35–58.

11. Kaur, I.P., Kanwar, M., 2002. Ocular preparations: the formulation approach. Drug Dev. Ind. Pharm. 28, 473–493.

12. Doane, M.G., Jensen, A.D. and Dohlman, C.H. (1978) penetration routes of topically applied eye medicines. Am. J. Ophthalmol. 85, 383-386.

13. Sasaki, H., Ichikawa, M., Kawakami, S., Yamamura, K., Mukai, T., Nishida, K., Nakamura,

J., 1997a. In situ ocular absorption of ophthalmic b-blockers through ocular membranes in albino rabbits. J. Pharm. Pharmacol. 49, 140–144.

14. S Asaki, H., Yamamura, K., Mukai, T., Nishida, K., Nakamura, J., Nakashima, M., Ichikawa, M., 1999. Enhancement of ocular drug penetration. Crit. Rev. Ther. Drug carrier syst. 16, 85–146.

15. J Arvinen, T., Jarvinen, T., Urtti, A., 1995. Ocular absorption following topical delivery. Adv. Drug. Deliv. Rev. 16, 3–19.

16. S Choenwald, R. D., Huang, H.-S., 1983. Corneal penetration behaviour of b-blocking agents i: physicochemical factors. J. Pharm. Sci. 72, 1266–1272.

17. A Shton, P., Podder, S. K., Lee, V. H. L., 1991. Formulation influence on conjunctival penetration of four beta blockers in the pigmented rabbit: a comparison with corneal penetration. Pharm. Res. 8, 1166–1174.

18. W Ang, W., Sasaki, H., Chien, D.-S., Lee, V.H.L., 1991. Lipophilicity influence on conjunctival drug penetration in the pigmented rabbit: a comparison with corneal penetration. Curr. Eye Res. 6, 571–579.

19. S Asaki, H., Igarashi, Y., Nagano, T., Yamamura, K., Nishida, K., Naka- Mura, J., 1995. Penetration of b-blockers through ocular membranes in albino rabbits. J. Pharm. Pharmacol. 47, 17–21.

20. S.C. Gad. Drug safety evaluation. Wiley, new york, 2002, pp,1-3.

21. Grass, Gm, Robinson, JR. (1988) mechanisms of corneal drug penetration. I: in vivo and in vitro kinetics J Pharm Sci 77,3-14

22. Grass, Gm, Robinson, JR. (1988) mechanisms of corneal drug penetration. Ii: ultrastructural analysis of potential pathways for drug movement j pharm sci 77,15-23

23. Sieg, Jw, Robinson, JR. (1975) vehicle effects on ocular drug bioavailability i: evaluation of fluorometholone j pharm sci 64, 931-936

24. Lee. V.h.l. and Robinson. JR. (1986) review: topical ocular drug delivery: recent developments and futurechallenges. J. Ocul. Pharmacol. 2, 67-108.

25. Greaves. J. l., Olejnik. 0. and Wilson, C. G. (1992) polymers and the precorneal tear film. Stp Pharm. Sci. 2, 13-33.

26. Urtti, A and Salminen, l. (1993) minimizing systemic absorption of topically administered ophthalmic drugs. Surv. Ophthalmol. 37, 435-456.

27. Tomi J & Vinen, Kristiina Jarvinen. Prodrugs for improved ocular drug delivery. Advanced drug delivery reviews, 19 (1996) 203-224.

28. Patton, T. F. and Robinson, J. R., quantitative precorneal disposition of topically applied pilocarpine nitrate in rabbit eyes. J. Pharm. Sei., 65 (1976) 1295.

29. Lee, V. H. L., precorneal, corneal, and postcorneal factors. In Mitra, A.K. (ed.), ophthalmic drug deliver), systems, Dekker, New York, 1993a, pp. 66-69.

30. Lee, V.H.L., improved ocular delivery by the use of chemical modification (prodrugs). In edman, p. (ed.), biopharma-ceuties ~f ocular drug deliver), CRC press, Boca Raton, 1993, pp. 121-143.

31. Liaw, J and Robinson, J. R., the effect of polyethylene glycol molecular weight on corneal transport and the related influence of penetration enhancers. Int. J. Pharm., 88 (1992) 125 140.

32. Liaw, J. and Robinson, J.R., ocular penetration enhancers. In Mitra, A.K. (ed.), ophthalmic' drug delivery systems, Dekker, New York, 1993, pp. 369 381.

33. Burstein, N.L. and Klyce, S. D., electrophysiologic and morphologic effects of ophthalmic preparations on rabbit cornea epithelium. Invest. Ophthalmol vis. Sci., 16 (1977) 899-911.

34. Chiou, G.C.Y. and Chuang, C., improvement of systemic absorption of insulin through eyes with

absorption enhancers. J. Pharm. Sci., 78 (1989) 815-818.

35. Green, K. and Tonjum, A., the effect of benza-lkonium chlo-ride on the electropotential of the rabbit cornea. Actaophthalmol., 53 (1975) 348 357.

36. Rojanasakul, Y., Liaw, J. and Robinson, J.R., mechanisms of action of some penetration enhancers in the cornea: laser scanning confocal microscopic and electrophysiology studies. Int. J. Pharm., 66 (1990) 131 142.

37. Saettone, M.F., Chetoni, P., Cerbai, R. and Mazzanti, G., effect of different enhancers on in vitro transcorneal penetration of drugs. Proc. Int. Symp. Control. Rel. Bioact. Mater., 21 (1994) 591 592.

38. Sasaki, H., Igarashi, Y., Nagano, T., Nishida, K. and Nakamura, J., different effects of absorption promoters on corneal and conjunctival penetration of ophthalmic beta-blockers. Pharm. Res., 12 (1995b) 1146 1150.

39. Bodor, N.. Eikoussi, A., Kano. M. and Nakamura, T. (1988) improved delivery through biological membranes. 26. Design, synthesis, and pharmacological activity of a novel chemical delivery system for, & adren-ergic blocking agents. J. Med. Chem. 31, 100-106.

40. El-koussi, A. and Bodor. N. (1980) formation of propanol in the iris-ciliary body from its propanol ketoxime precursor - a potential antiglaucoma drug. Int. J. Pharm. 53, 189-194.

41. Polgar. P. and bodor, N. (1095) minimal cardiac electro-physiological activity of alprenoxime, a site-activated ocular p-blocker. In dogs. Life Sci. 56, 1207-1213.

42. Mosher, G. L. and Mikkelson, T. J. (1979) permeability of the alkyl p-aminobenzonate esters across the isolated cornea1 membrane of the rabbit. Int. J. Pharm. 2, 239-243.

43. Suhonen, P., Jlrvinen, T., Peura, P. and Urtti, A. (1991) permeability of pilocarpic acid diesters across albino rabbit cornea in vitro. Int. J. Pharm. 74, 221-228.

44. Suhonen, P., Jarvinen, T. Rytkonen, P.. Peura, P. and Urtti. A. (1991) improved cornea1 pilocarpine per-meability with o,o′-(1,4-xylylene) bispilocarpic acid ester double prodrugs. Pharm. Res. 8. 1539-1542.

45. Redell. M. A., Yang, D. C. and Lee, V. H. L. (1983) the role of esterase activity in the ocular disposition of dipivalyl epinephine in rabbits. Int. J. Pharm. 17, 299-

46. Weinkam, R. J., Waldemussie. E.. Ruiz, G.. Feldmann, B.. Dino. J., Ismail, I. and Bundgaard, H. (1990) pilocarpine prodrugs: 0-benzoyl pilocarpic acid methyl ester ocular metabolism and effects on miosis and intraocular pressure. Pharm. Res. (suppl.) 7, 64.

47. Grove. J., Gautheron, P., Plazonnet, B. and Sugrue, M.F. (1988) ocular distribution studies of the topical carbonic anhydrase inhibitors l-643,799 and l-650,719 and related alkyl prodrugs. J. Ocul. Pharmacol. 4. 279-290.

48. Schoenwald, R.D. and Barfknecht, Cf. (1991) prodrugs of carbonic anhydrase inhibitors. Eur. Patent Appl. 0 419 311 a2.

49. Colla, l. De Clercq. E., busson, R. And Vanderhaeghe. H. (1983) synthesis and antiviral activity of water-soluble esters of acyclovir [9-[(2-hydroxy-ethoxy)methyl]guanine]. J. Med. Chem. 26, 602-604.

50. Narurkar, M.M. and Mitra. A.k. (1989) prodrugs of s-iodo-2′. Deoxyuridine for enhanced ocular transport. Pharm. Res. 6. 887-891.

51. Musson, D., Bidgood, A. and Olejnik, 0. (1989) in vitro penetration and metabolism studies of pred-nisolone phosphate, disodium and prednisolone acetate across the cornea of rabbits. Pharm. Res. (suppl.) 6. S-175.

63. Broer, S, Wagner, CA, Lang, F. (2001) function and structure of heterodimeric amino acid transporters Am J Physiol 281, c1077-c1093

64. Palacin, M, Estevez, R, Bertran, J, et al (1998) molecular biology of mammalian plasma membrane amino acid transporters Physiol Rev 78, 969-1054

65. Deves, R, Boyd, CA. (1998) transporters for cationic amino acids in animal cells: discovery, structure, and function Physiol Rev 78, 487-545

66. Kekuda, R, Torres-Zamorano, V, Fei, YJ, et al (1997) molecular and functional characterization of intestinal Na+-dependent neutral amino acid transporter b0 Am J Physiol 272, g1463-g1472

67. Torrents, D, Estevez, R, Pineda, M, et al (1998) identification and characterization of a membrane protein (y+l amino acid transporter-1) that associates with 4f2hc to encode the amino acid transport activity y+l: a candidate gene for lysinuric protein intolerance J Biol Chem 273, 32437-32445

68. Pfeiffer, R, Rossier, G, Spindler, B, et al (1999) amino acid transport of y+l-type by heterodimers of 4f2hc/cd98 and members of the glycoprotein-associated amino acid transporter family Embo J 18, 49-57

69. Anand BS, Mitra AK. Mechanism of corneal permeation of l-valyl ester of acyclovir: targeting the oligopeptide transporter on the rabbit cornea. Pharm Res. 2002, 19, 1194-1202.

70. Jain-vakkalagadda B, Pal D, Gunda S,Nashed Y, Ganapathy V, Mitra A K. Identification of a Na+-dependent cationic and neutral amino acid transporter, b 0,+ in human and rabbit cornea. Molecular pharmaceutics. 2004, 1(5), 338-346.

71. Anand BS, Katragadda S, Nashed YE, Mitra AK. Amino acid prodrugs of acyclovir as possible antiviral agents against ocular hsv-1 infections: interactions with the neutral and cationic amino acid transporter on the corneal epithelium. Curr Eye Res. 2004 aug-sep; 29(2-3): 153-66.

72. Majumdar S, Nashed YE, Patel K, Jain R, Itahashi M, Neumann DM, Hill JM, Mitra AK. Dipeptide monoester ganciclovir prodrugs for treating hsv-1-induced corneal epithelial and stromal keratitis: in vitro and in vivo evaluations. J Ocul Pharmacol Ther. 2005 dec; 21(6): 463-74.

73. C. U. Nielsen, J. Va°benø, R. Andersen, B. Brodin, B. Steffansen, recent advances in therapeutic applications of human peptide transporters, expert opin. Ther. Patents 15 (2005) 153–166.

74. C. U. Nielsen, A. Andersen, B. Brodin, S. Frokjaer, M.E. Taub, B. Steffansen, dipeptide model prodrugs for the intestinal oligopeptide transporter. Affinity for and transport via hpept1 in human intestinal caco-2 cell line, j. Control. Release 76 (2001) 129–138.

75. P. V. Balimane, P. J. Sinko, involvement of multiple transporters in oral absorption of nucleosides analogues. Ad. Drug Deliv. Rev. 39 (1999) 183-209.

76. Y. h. Li, M. Tanno, T Itoh, H. Yamada. Role of monocarboxylic acid transport system in the intestinal absorption of an orally active beta lactam prodrug: carindacillin as a model, int. J.pharm. 191 (1999) 151-159.

77. Y. lu, P. S. Low, folate mediated delivery of macromolecular anticancer therapeutic agents. Adv. Drug deli. Rev. 54(2002) 675-693

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Mini Review Articles

AUTOMATED DISPENSING: AN OVERVIEW

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ABSTRACT

Promptness of medicine preparation is one of the important tasks the pharmacy has to tackle. A new automated dispensing system has been developed in order to adopt parallel preparation of the prescription. The system consists of a large LAN system, which is connected to a host-computer, control-computer, automatic preparation machines and conveyer lines. The prescription data issued by each physician are first audited by the host computer and then used as the date for preparation. Prepared data checked by pharmacists are delivered to the manual preparation station (tablets, powder, topical drugs, and solutions) as a preparation instruction sheet and transmitted directly to the automatic preparation machines (e.g. medicine bag printing machines and automatic tablet dispensing and packaging machines). In collecting the prepared medicines, a controlled conveyer line was established. The waiting time decreased significantly after the system was introduced. This system not only reduces actual medicine preparation time but also improves the progress of the dispensing operation efficiency.

INTRODUCTION

The increased demand for the utilization of hospitals, together with the growing shortages (felt especially in the United States of America) of professional personnel nurses, pharmacists, dieticians and social workers stimulated through and research work in simplification through establishment of criteria which define each and every job performed by this category of personnel. It was felt in United States of America that a great deal of nursing time was consumed by the frequent trips to the pharmacy to obtain drugs (which is the situatuation still prevailing in our hospitals in India) and ancillary supplies. As a direct result of this situation, many administrators have requested the hospital pharmacist and nursing administrative staff to scrutinize present procedures and develop new systems for the dispensing of medicines.

In recent years, comprehensive hospital information systems have been developed that operate online to help in clerical work, medicine preparation, and clinical laboratory investigation through stand-alone computer systems. These systems have yielded specific improvements in the shortening of outpatients′ hospital stay time[1,2] and in the development and use of clinical databases. As health care environments grow increasingly complex, many institutions are turning to computer-driven systems to save the day. Automated technology is becoming a powerful component of health care as human resources become scarce and currently in use at a large general acute care hospital.

Automated dispensing systems are drug storage devices or cabinets that electronically dispense medications in a controlled fashion and track medication use. This new automated system assists the pharmacy department by packaging and dispensing medications to be used in the centralized, computer supported cart-filling process. An automated dispensing system installed in an acute hospital has halved dispensing errors, reduced the time needed to prepare medicines and ensures the correct dosage[3].

As hospital pharmacy faces a future of recruitment difficulties and increased throughput of patients, these automated systems could be extremely useful, not only in dispensing for discharged patients but also for outpatient and ward stock supplies. This article is mainly focused on advances in automation in dispensing of pharmaceuticals and its impact on present hospital pharmacy system.

OBJECTIVES OF DEVELOPMENT OF THE AUTOMATED DISPENSING SYSTEM

The objectives in developing this system are to

(1) Shorten patient waiting time

(2) Reduce dispensing errors

(3) Reduce labor time

(4) Simplify dispensing procedures

(5) Reduce workload in medicine preparation

ECONOMIC CONSIDERATION FOR THE SET UP OF AUTOMATED DISPENSING SYSTEM[4]

Establishing the price of an automated dispensing system requires detailed evaluation of each bid. The overall price will inevitably include both capital costs (costs of machine) and revenue and recurring costs (service cost). Important costs that should be determined and compared include:

- Capital costs of the machine and any additional components, such as refrigeration modules
- Payment terms
- Maintenance or service costs either per call out or per annum
- Additional training costs, if any
- Costs of integrating the pharmacy computer sys tem

WIRELESS DEVICES IN AUTOMATED DISPENSING

There will be an explosive increase in the use of wireless devices by healthcare professionals and by the general public. Although wireless devices currently create electromagnetic interference with powered wheelchairs, apnea detectors, hearing aids, infusion pumps, cardiac telemetry, cardiac pacemakers, and ventilators, it is expected that technological solutions, such as reducing power transmission levels and interference management, will enable these devices to be used in healthcare settings before 2020. As these devices proliferate, design challenges and opportunities will arise from the distributed nature of easily accessible information and software. For example, if a user controls a number of infusion pumps on multiple patients via a single device, how is the Interface designed to enable proper mapping to patients? Similarly, if two healthcare professionals "compare notes" on a patient can wireless devices support this interaction, by sharing information and standardizing information display to enable comparison?

It is not expected that a single wireless technology or device will meet all the design goals and address all the issues presented by users. Human factors engineers should be involved in every design project that includes wireless technology and the associated decisions that must be made to identify the most appropriate technologies for that application and human device-use model.

ADVANTAGES OF AUTOMATED DISPENSING[5]

- Drug acquisition time is reduced
- Accountability for controlled substances is strengthened
- Billing is improved
- Missing medications are decreased because a security code is needed to remove medications and because only drugs on the patient profile may be obtained.

LIMITATIONS OF AUTOMATED DISPENSING SYSTEM[6]

Although automated dispensing systems are beneficial in current dispensing practices in most of the hospitals, several practical limitations have been observed after the survey in some of the hospital pharmacy units in UK, includes nurses waiting at busy administration times, removal of doses ahead of time to circumvent waiting, and overriding the device when a dose was needed quickly.

IMPACT OF AUTOMATION IN CURRENT DISPENSING PROCESS[7,8]

As hospital pharmacy faces a future of recruitment difficulties and increased throughput of patients, these automated systems could be extremely useful, not only in dispensing for discharged patients but also for outpatient and ward stock supplies.

Staff shortages throughout hospital pharmacy caused by the fallow year, salary competition from community pharmacies and new posts being created within primary care groups and trusts mean that hospital pharmacists and technicians are becoming rare species. It is becoming even more important that they use their precious time on things that are really necessary. This means ensuring that the patient receives adequate pharmaceutical care before, during and after hospitalization. There are also the issues of increased workload and patient expectations. Both demand that more time be spent at the point of delivery of service-on the ward.

The dispensing process is eminently suitable for automation as long as there are sufficient checking procedures involved. The introduction of technician accuracy checking is an example of how the process can be changed without loss of effectiveness. The overall effect upon the staff structure will depend on the enlightenment of the pharmacy managers who may decide to follow this route. The emphasis of the current Government is on governance, risk management and technology. These are all good pointers in support of automated dispensing. Unfortunately, business cases are required and these need financial analyses. It has to be made clear that automated dispensing fills the gap caused by the inability to recruit in hospitals and should not be seen as a large staff reduction exercise. The impact of automation will be to release more of all grades of staff for "near patient" activities.

Three important changes have been introduced into hospital pharmacy in recent years: re-use of patients' own drugs; new ways of dispensing for discharge; and patient self-administration of drugs. These need intensive pharmacy input if the benefits are to be fully achieved, and only by transferring staff-intensive processes to machines can they be totally achieved. We are currently undergoing a period of skill mixing and matching to cope with the new enhanced clinical pharmacy role. This new role is defined as the comprehensive "near patient" pharmacy service, which will eventually need some help from the newer technologies, such as automated dispensing, in order for it to be successful. This was evident during the original development of clinical pharmacy, which was undoubtedly helped by the move away from handwritten and typewritten labels to computerized labelling in the 1980s. Time became released to extend "topping-up" services and clinical pharmacy.

CONCLUSION

As hospital pharmacy faces a future of recruitment difficulties and increased throughput of patients, these automated systems could be extremely useful, not only in dispensing for discharged patients but also for outpatient and ward stock supplies. Implementation of automated dispensing reduces personnel time for medication administration and improves billing efficiency, reduction in medication errors have not been uniformly realized. Indeed, some studies suggest that errors may increase with some forms of automation. But the overall effect of automated dispensing is very beneficial in modern trend of dispensing. Implementation of an automated check-and-sortation device in a correctional health care system appeared to reduce dispensing errors and give pharmacists more time to review patient profiles and recommend clinical interventions. Although automated dispensing systems are increasingly common, it appears they may not be completely beneficial in their current form. Further study is needed to demonstrate the effectiveness of newer systems such as the Omnicell automated dispensing devices.

REFERENCES

1. Masuda H, Asami K, Kobayashi Y, Suga M, Tnaka S, Tamura T, Katoh M, Skazume S, Arakawa K, Sasahara H, Onoda G, Ymashita T, Ono M, Tsutsumi Y, Nunokawa N, Homma S, Chugun E, Kosugi K, Satoh H, Igarashi K, Tanno K, Comparison and estimate of waiting times in traditional (previous) and computerized pharmacy systems, Jpn J Hosp Pharm, 17, 1991, 211-217.
2. Higuchi K, Tsukamoto T, Nakano S, Sakai S, Morikawa N, Takeyama M, Development and estimation of management system for dispensing, Jpn J Hosp Pharm, 18, 1992, 584-593.
3. Ishizuka H, Horiguchi M, Waki Y, Maeda M, Ishikura C, Computerized dispensing system: reducing the time of dispensing medicines, Int J Biomed Comput, 28, 1991, 137-146.
4. Fitzpatrick R, Automated dispensing-developing a business case to support investment, Hospital Pharmacist, 11, 2004, 109-111.
5. Janet Carmenates and Matthew R. Keith, Impact of Automation on Pharmacist Interventions and Medication Errors in a Correctional Health Care System, Am J Health-Syst Pharm, 58(9), 2001, 779-783,.
6. Allan Karr, Automated Dispensing-Procuring automated picking and storage systems, Hospital pharmacist, 11, 2004, 152-154.
7. Freeborn S, Automated dispensing - the impact on the workforce. Hospital Pharmacist 7(9), 2000, 238.
8. Slee A, Farrar K, Hughes D, Implementing an automated dispensing system, Pharmaceutical Journal, 268, 2002, 437-438.