CELLULAR TRANSPORT MECHANISMS IN ACTION OF COLLOIDAL DELIVERY SYSTEMS

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Creation of modern highly effective drugs and cosmetics is based not only on inclusion in formulations of new highly effective biologically active substances (BAS). A perspective direction is use in formulations special delivery systems, providing transport of well known active principles across organism barrier structures to molecular targets and thus increasing efficiency of preparations. Most of delivery systems are different kinds of colloidal dispersions with BAS, incorporated in dispersion medium structures (particles, drops, micelles, networks, etc.). Corpuscular structure of BAS carrier in colloidal delivery system and tissue organization of barriers in organism make insufficient explanation of delivery effects by diffusion. Tight junctions between cells in epithelium and endothelium prevent the passage even of molecules and ions through the intercellular space and so corpuscular materials must actually enter the cells in order to pass through the tissue.

Thus, action of colloidal delivery systems mast involves cellular transport mechanisms, such as endocytosis (pinocytosis), transcitosis and exocytosis. Involving of those processes in delivery of BAS by colloidal particles is in accordance with fact, that nanosize delivery systems are more effective, since inclusion of particles with size lower 300 nm by cells is more intensive, nonspecific

and inherent to all eukaryotic cells. Usually this type of endocytosis classified as pinocytosis. But stated above scheme explains delivery mechanisms in case of suspensions and oil in water colloidal systems with stable in water dispersed medium structures. For water in oil systems such explanation is mismatching. In this case solution of BAS release from internal disperse medium in to cells surrounding and so cause of stimulation of BAS accumulation in cells is different. Most probably it is in fractional realizing of contents of disperse medium structures, which result in fluctuations of BAS concentration around cells and simulate intercellular exchange of substances and signaling. Activation of pinocytosis and accumulation of surrounding medium components in cells as result take place.

An interesting direction in creation of drug delivery systems is multilevel disperse colloidal systems - multiple water-in-oil-in-water (W/O/W) emulsions. Distinctive characteristic of such systems is resemblance to living cell. On the one hand in these systems drops of secondary emulsion are structured with droplets of internal water similar to cellular compartmentalization. On the other hand when such structured particles release BSA from internal water medium in surrounding, its occur according above described schema as intercellular communications. Ability of silicones to dissolve significant amounts of oxygen and carbonic gas make silicone liquids attractive for use as oil medium in this emulsion model of cells. Owing to gases dissolving ability of silicone oils are also attractive for use in transdermal delivery systems, because silicone occlusion of skin is gas permeable and so may consider as more physiological even then occlusion with natural oils.

In this work W/O emulsion as primary for multiple W/O/W emulsions with silicone liquids as oil medium was investigated. An ability of such W/O emulsions to provide effective intra- and transdermal transport of hydrophilic BAS was shown in experiments on laboratory animals. For intradermal delivery estimation riboflavin (vitamin B_2) model was used. In these experiments significant acceleration of vitamin penetration into CFW male mouse skin was observed after emulsion application against water solution and gel composition. Besides more intensive inclusion of riboflavin in skin cells multienzyme complexes took place after application of emulsion. Transdermal delivery was investigated in experiments with registration of systemic effect of *Hypericum perforatum* extract. Estimation of Wistar rats behavior after skin application of W/O emulsion with this extract in water medium have shown significant decreasing of animals aggressiveness and anxiety. So, investigated type of emulsions is effective both intradermal and transdermal delivery system.

As mentioned above in most pharmaceutical and cosmetic formulations W/O emulsion transform in to secondary multiple W/O/W emulsions. In our light microscopic investigations of such formulations we found self organization of Brownian motion of internal water medium droplets inside secondary emulsion drops. This motion has the appearance of circulation and is stable during several tens of minutes after microscopic specimen preparation. Discovered phenomenon is interesting not only for understanding of delivery mechanisms, but may help to make clear principles of cell motility.