the lower is the rate of diffusion. Particle size not only affects rate of diffusion and absorption of drugs injected IM or SC but also affects the degree of re-suspension prior to injection and the syringeability/injectability of the suspended product. It is important not only to control the size of particles but also the size range. The smaller the particle size and range, the better will be the ability to resuspend, withdraw and inject the dose, and the rate of absorption at the injection site.

Viscosity

Viscosity is the resistance to free flow and is used to affect rate of absorption of IM and SC injections and topically applied ophthalmic medications. Depot formulations, using single or combination of polymers, in part, rely on viscosity effects of these large molecules to retard to the diffusion flow of the drug from the depot to the circulation. Topically applied ophthalmic medications usually contain viscous vehicles; for example, hydroxypropyl methylcellulose or polyvinyl alcohol, to adhere to the corneal epithelium for a longer time than solutions would otherwise without these polymers present, with the increased contact time allowing for more drug to be absorbed.

Solid State Morphology

In injectable suspensions, drugs exist as crystalline or amorphous solid state entities or mixtures of these states. The solid-state morphology will affect the rate of solution of these solid molecules. Crystalline drugs are known to have dissolution rates slower than the same drug in the amorphous state. Insulin is a great example of an important injectable drug that can be formulated as either completely amorphous (Semi-Lente formulations), completely crystalline (Ultra-Lente formulations), or combinations of crystalline and amorphous states (Lente). Each of these formulations have different rates of insulin release and availability with the amorphous Semi-Lente suspensions having the faster release rates and the crystalline Ultra-Lente having the slowest release rates.

Osmolality

Injectable products ideally should be iso-osmotic with biological fluid, and most commercial products are iso-osmotic in order to minimize pain and tissue irritation upon injection. Large differences in osmolality can effect passive diffusion. Hypotonic (hypo-osmotic) solutions will cause movement of the product solvent away from the site of injection since by the law of osmosis, product solution will move from a region of lower concentration to a region of higher concentration to equalize pressure on both sides of the biologic membrane. This movement of product solvent will cause drug concentration to increase at the injection site and the rate of passive diffusion will increase. The opposite phenomenon will occur with drug injections that are hypertonic (hyperosmotic) where the fluid from biological cells will flow to the drug solution to equalize pressure and drug concentration, and passive diffusion rate will decrease. Obviously isotonic formulated injectable products will have no effect on fluid movement and no effect on drug diffusion.

Injection Volume

Injection volume matters for all routes of administration except for intravenous. Fick's Law shows that diffusion rate is inversely proportional to injection volume [$dq/dt = K\ (A/V)$]; therefore, more rapid absorption is generally obtained when drugs are administered in smaller injection volumes. The larger the injection volume for injections within confined areas, e.g., IM/SC, capillary beds in the region will be compressed and the tissue surface area to volume ratio will be lowered. Since passive diffusion is directly proportional to surface area (A), larger injection volumes will decrease the rate of diffusion. Excessively large injection volumes in confined areas of the body will also increase local pressure and induce unnecessary pain. Table 31-2 provided the usual volume of injection based on site of injection. For IM injections in different muscle groups, the maximum volume given in the gluteus maximus region is 5 mL while only 2 mL is given in the deltoid muscle of the shoulder.