1. Aim of Present Work

It is estimated that approximately 40% or more of the new chemical entities (NCE) generated through drug discovery programs are poorly soluble in water. Formulation of this class of compounds is a challenging problem faced by the pharmaceutical researcher, because typical problems associated with these drugs are a too low oral bioavailability and erratic absorption due to their too low saturation solubility and dissolution velocity. For oral administration, the low concentration gradient between the gut and blood vessel due to the poor solubility of the drug leads to a limited transport, consequently influences the oral absorption. [1]

The poorly soluble drugs with relatively high permeability through CaCo-2 cell monolayer's, which warrant it to be classified under BCS Class II classification. For poorly soluble drugs as seen in BCS Class II, the dissolution of the drugs in the gastrointestinal fluid media is the rate limiting step for the absorption of the drugs.[2] The poor aqueous solubility may result in irreproducible results or therapeutic failure in some cases due to sub therapeutic plasma level concentrations. The dosage forms are often times affected by the fed-fasted state of the patient and its onset of action is slower than anticipated.[3]

Hence for efficient absorption of drugs from the gastrointestinal tract for improving their therapeutic efficacy, there is an imminent need for studies in designing novel strategies for their dissolution enhancement.

The basic challenge faced by the researcher for the formulation of such poorly soluble drugs is the low oral bioavailability and erratic absorption of the drugs from the gastrointestinal tract due to their low saturation solubility and dissolution velocity. The low saturation solubility results in a low concentrtion gradient between the gut and blood vessel and leads to a limited transport of drug.[4]

There are number of techniques like liposomes[1], emulsions, microemulsions[5], solid-dispersions[6] and inclusion complexes using cyclodextrins[7] show reasonable success but they lack in universal applicability to all drugs.[8] Micronization is used to improve dissolution velocity of poorly soluble drugs but reducing the drug to micron size does not increase the saturation solubility of the drug, and at such a low saturation solubility, the increment in the dissolution characteristics does not help to a great extent[9].

Hence there is a need for development an economic and a universal approach applicable to all poorly soluble drugs. Novel drug delivery strategies such as nanosuspensions, nanoemulsions etc, could be studied for dissolution enhancement of such drugs. [10-11]

Hypertension is one of the common cardiovascular disorders of modern times. According to WHO, hypertension is currently defined as when SYSTOLIC PRESSURE is consistently greater than 140 mm Hg or when DIASTOLIC PRESSURE is consistently 90 mm Hg or more.

Epidemiologic studies indicate that the risks of damage to kidney, heart, and brain are directly related to the extent of blood pressure elevation. Even mild hypertension (blood pressure 140/90 mm Hg) in young or middle-aged adults increases the risk of eventual end organ damage. Elevated blood pressure is usually caused by a combination of several abnormalities (multifactorial). Epidemiologic evidence points to genetic inheritance, psychological stress, and environmental and dietary factors (increased salt and decreased potassium or calcium intake) as perhaps contributing to the development of hypertension. Many oral antihypertensive agents such as diuretics, β adrenergic receptor antagonists, α_1 adrenergic antagonists, Ca^{2+} channel antagonists, angiotensin-converting enzyme inhibitors, vasodilators, are available for the treatment of hypertension. [12]

First identified in the late 1960s, calcium channel blockers (also called CCBs or calcium antagonists) are non-habit-forming medications that are used to relax the smooth muscles of the arteries and arterioles as well as the heart muscle, which reduces the workload on the heart and causes a drop in blood pressure. Compared with other classes of antihypertensive agents, there is a greater frequency of achieving blood pressure control with Ca2+ channel blockers as monotherapy in elderly subjects.[13]

Nifedipine, Nimodipine and Nitrendipine a highly potent calcium-channel blocker belonging to the group of dihydropyridines widely used in the treatment of vascular diseases such as hypertension, angina pectoris and anti-atherosclerotic activity are classified as a Class II API (poorly soluble and highly permeable) by the Biopharmaceutics Classification System (BCS)[14-16]. Hence the dissolution of the drugs in the gastrointestinal fluid media is the rate limiting step for the absorption of these drugs.

In light of this present investigation, novel drug delivery strategies such as nanosuspensions prepared by milling technique and nanoprecipation were studied for dissolution enhancement of such BCS class II poorly soluble drugs Nifedipine, Nimodipine and Nitrendipine.

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