Chapter-13

Summary and Conclusion

Inclusion compounds are defined as *the compounds formed by inclusion of one kind of molecules,* called guest molecules, *into cavities of a crystalline framework composed of the molecules of another kind* (or into a cavity of one large molecule) called the host molecule, *without forming any specific chemical bonds between the guest and host.* Unlike the case of traditional chemical compounds, favorable spatial complementarity of the guest and host subsystems, not chemical reactivity, plays the important role in the formation of these compounds from the components. The principle of formation allows formation of supramolecular crystalline phases that are thermodynamically more stable than the mixture of initial components.

The wide ranging interest in inclusion compounds has a theoretical and practical background. Properties of inclusion compounds have been a focus of attention, in view of the propensity of altered physiochemical, structural, and dynamic properties of the systems. The number and types of adductors, belonging to diverse chemical categories identified mostly through by chance and some via directed synthesis have grown tremendously. Among the adductors *which have been extensively investigated and put into commercial use because of their unique property of formation of inclusion compounds are urea, cyclodextrins, zeolites, graphite, hydroquinone, phenols, water hydrates* etc. Among these adductors, cyclodextrins, however, deserve a special mention as these are the most extensively exploited complexing agents in pharmaceutical drug development. There are more than 30 products in the pharmaceutical drug market which have been formulated using cyclodextrins as a complexing agent. Inclusion of drugs in cyclodextrins offer numerous distict advantages as per the following:

- Improved dissolution profile and bioavailability
- Enhanced photo-stability
- Reduced air-senstivity/hygroscopicity
- Reduced volatilization/ sublimation of drugs
- Increased shelf life
- Reduced side effects like irritation
- Improved content uniformity
- Liquid injectable solutions from poorly soluble drugs
- Improved acceptability of drug due to masking of unpleasant odour or taste

- Imparting safe handling characteristics to hazardous drug
- Prevent drug-drug or drug-additive interactions
- Convert oils and liquid drugs into microcrystalline or amorphous powders
- Impart sustained drug release profile

Some of the important examples of drugs complexed with different derivatives of cyclodextrins and being marketed now-a-days as cyclodextrin complexed form are piroxicam, cisapride, chloramphenicol, diclofenac sodium, itraconazole, ziprasidone, variconazole, mitomycin, nitroglycerine, iodine, chlordiazepoxide to name a few.

On the contrary, there is not a single pharmaceutical product in the market based on adductors other than cyclodextrins. Urea as an adductor has been extensively investigated for its wide ranging structural, dynamic and conformational properties. Urea adduction has been exploited extensively as a powerful technique for isolation of alpha olefins and normal olefins from various petroleum fractions and appropriate machinery plant dedicated solely to carry out this separation have been erected by major oil giants. Urea adduction has also been utilized for isolation of free fatty acids from different animal and vegetable oils and for laboratory scale chromatographic procedures. However, till date the *urea adduction process has not been exploited by pharmaceutical industry for the development of any pharmaceutical formulation.*

The serendipitous discovery of formation of urea inclusion compounds by Bengen during World War I revealed a new aspect of the small urea molecules. Urea inclusion compounds have attracted considerable attention since then and are still a focus of extensive research. It is now well established that urea forms channel like inclusion compounds with all long-chain organic molecules provided some critical value of molecular length is exceeded. Urea molecules form an extensively hydrogen-bonded honey-comb network containing parallel helical tunnels with diameter between 5.5-5.8 Å and tunnel centers separated by *ca* 8.2 Å. The walls of tunnels are covered with the smooth faces of urea molecules into two helical ribbons running in opposite directions. A wide variety of guest molecules, among which are not only *n*-alkanes, *n*-alkenes and their derivatives but also linear polymers, pack into the tunnels. The minimum chain length

required for inclusion of a given class of guest molecules depends strongly upon the size, polarity and the position of the substituents. Guest molecules interact only weakly with the channel walls and undergo substantial translational and vibrational motions along the tunnel axis.

Urea is known as an adductor for linear compounds, and is not known to form adducts with cyclic substituted organic compounds under any known conditions. However, urea does form adduct with substituted cyclic organic compounds provided there is a long chain substituent to the ring. The long chain of this compound is readily adducted and apparently the unit cell can easily withstand the distortions caused by an occasional benzene groups. Also, 3-methyl heptane, which is normally a non-adductible endocyte (NNAE), forms an adduct with urea only when a slenderer hydrocarbon (e.g. n-C_6H_{14}) –a rapidly adductible endocyte (RAE) serves as a *pathfinder.*

Thus, the co-inclusion of a NNAE in presence of RAE in urea lattice was reported in literature (1949) but never investigated further. However, in 1993, the aforementioned reports were exploited, by Madan and Grover, for co-inclusion of Vitamin A palmitate in urea in the presence of a suitable RAE resulting in improved pharmaceutical characteristics of Vitamin A palmitate. Later, Bajaj and Madan patented urea inclusion formation as a process for converting liquid Vitamin E into free flowing crystalline powder having improved stability and better dissolution profile. However, there are no further reports of exploitation of aforementioned technique for improvement for pharmaceutical characteristics of drugs and till date; there is not even a single product available in the market based on the said technique.

In the present study, an attempt has been made to include normally non-adductible endocytic (NNAE) drugs in urea through modified technique for the improvement of pharmaceutical characteristics like the dissolution profile, content uniformity, improved handling characteristics and protection from photo- and air-degradation.

The NNAE drugs are not known to form adduct in urea under any known conditions, due to presence of cyclic and/or substituted moieties in their molecular structure. However, in the presence of a suitable RAE, NNAE drug co-adducts and formation of mixed crystals results. Presence of either cyclic and/or highly branched groups in NNAE drug results in the local distortion of unit cells of hexagonal urea in the vicinity of the cyclic/aromatic ring. These distortions of unit cells of hexagonal urea will lead to reduced stability of the resulting inclusion compound. This reduction in stability is manifested as decrease in heat of crystalline transition from the hexagonal urea to tetragonal one releasing the contained endocyte.

Urea, an extremely water soluble moiety, tends to dissolve instantaneously upon incorporation of a urea inclusion compound to aqueous medium. The breakdown of hexagonal lattice will result in rapid and instantaneous release of included drug into the aqueous medium. Since the drug is already at molecular level, release of drug from the distorted lattice is expected to result in almost instantaneous release of medicament. Moreover, the guest moiety is shielded from effect of atmospheric oxidation, when enclosed in a network of host molecules. Further as the guest molecule is entrapped within the host framework, there is restricted movement along bond axis leading to reduced possibility of photoisomerisation. Hence, *urea based inclusion complexes of drugs in presence of a suitable rapidly adductible endocyte can be characterized by improved solubility and stability profile.*

Development of mathematical models for prediction of adductability in urea:

The present work pertains to development of mathematical models for prediction of adductability in urea of a diverse range of aliphatic and cyclic substituted organic compounds. Thus the exhaustive data available on adductability of compounds was extracted and compiled from literature and segregated into two sets, one set comprising of all branched aliphatic compounds and second set of cyclic substituted compounds. *Wiener's index*—a distance-based topological descriptor, *molecular connectivity index*, an adjacency-based topological descriptor and *eccentric connectivity index*—an adjacency-cum-distance based topological descriptor were employed for the present study. For branched aliphatic compounds, the data set comprising of 133 compounds was

further segregated randomly into training and test set. The values of all the three topological indices for all the compounds constituting the training and test sets were computed using an in-house computer program. Resulting data of thetraining set was analyzed and suitable models were developed after identification of the adductible ranges. Subsequently,each compound in the training set was either classified as adductible or non-adductible using these models, which was then compared with the reported adductability in urea. An accuracy of prediction of ≥86% was observed using models based on the three topological descriptors in the training set. These models were then cross-validated using test set. An accuracy of prediction was of ≥ 80% was observed during cross-validation of these models in an independent test set.

Similarly, relationship of urea adductability for a dataset of 45 cyclic organic compounds was studied and suitable models were developed for prediction of adductability in urea using aforementioned topological descriptors. Accuracy of prediction was found to vary from a minimum of ~ 90% for a model based upon eccentric connectivity index to a maximum of ~92% for model based upon Wiener's index.

Selection of suitable drug candidates:

The literature was extensively reviewed for selection of suitable NNAE potent drug candidates which could be successfully co-included in urea using the modified technique. A model drug candidate was required to be orally active, low dose drug having limited water solubility, compliance with steric requirements and instability in solid state manifested either as atmosphere or light sensitivity. On retrofit analysis of the data, following drugs were selected for the present study

Amiloride hydrochloride (AH): Amiloride hydrochloride (AH) is a potassium sparing diuretic, with relatively weak natriuretic and anti-hypertensive activity. The solubility of AH in water is typical of an organic base with limited aqueous solubility, which increases with a decrease in pH. It has been shown using radiolabelled AH that approximately 50% of an oral dose administered to man is absorbed from gastrointestinal tract. The remainder of the dose unabsorbed and is found in the feces. *Though as per USP, Amiloride Hydrochloride is a slightly water soluble drug, but the same has been classified as BCS class I. This may be attributed to the fact that dose of the drug happens*

to be within the solubility limits. However, complexation with urea is naturally bound to significantly improve its dissolution profile leading to improved bioavailability.

Enalapril maleate (EM): Enalapril maleate is highly effective antihypertensive agent, which act as angiotensin converting enzyme inhibitors. Enalapril acts as a prodrug; following oral administration it is bioactivated by hydrolysis of the ethyl ester to enalaprilate, which is the active ACE inhibitor. Though as per BP, Martindale, the Extra Pharmacopoeia, enalapril maleate is a *slightly water soluble drug, dose of the drug happens to be within the solubility limits and hence, the drug is classified as BCS class I.* However, complexation with urea is bound to significantly improve dissolution profile of the drug, leading to instantaneous release of the drug and to improved bioavailability culminating to immediate relief to a hypertensive patient.

Glipizide (GLP): A second generation sulphonylurea that lowers the blood glucose level in humans by stimulating the release of insulin from the pancreas and is typically prescribed to treat non-insulin dependent diabetes mellitus. Glipizide, being insoluble in water, belongs to *BCS class II* and its dissolution is considered to be a rate-determining step in its absorption from the gastro-intestinal fluids. Recently, attempts have been made to study detailed solubility/dissolution profile of GLP and to improve its dissolution behavior using cyclodextrin inclusion compounds or as solid dispersion in water-soluble carriers. An attempt has been made in the present study for *steep enhancement of dissolution rate of GLP* through formation of co-inclusion compounds of GLP in urea using a modified technique.

Cis-retinoic acid (*Cis*-RA): 13-*cis* retinoic acid or *cis*-retinoic acid (*cis*-RA) is a synthetic retinoid, which has found clinical applications by systemic therapy for the treatment of severe calcitrant cystic acne vulgaris and in the cases of persistent and recurrent moderate acne. *Cis*-RA is a lipophilic drug and is sparingly soluble in water. It is poorly absorbed after oral administration and is advised to be taken with food. In general, retinoids are unstable compounds, being sensitive to oxygen, heat, and light. Their stability is, therefore, of pharmaceutical interest. Therefore, the development of novel formulations characterized by improved dissolution profile and reduced sensitivity towards retinoic acid photoisomerisation seems to be important. Moreover, *cis*-RA is regarded as hazardous drug and requires safe handing by personnel involved with preparation,

processing, administration and disposal of the drug. It is strongly recommended that personnel should wear gloves and adequate necessary clothing while handling the drug. *Hence, urea inclusion compound formation is proposed to impart safe handling characteristic to cis-RA in addition to simultaneous improvement in the dissolution profile and photostability.*

Nicorandil (NRD): A potassium channel activators, has coronary vasodilative and coronary vasoconstriction suppressing actions and is useful as a curative for various types of angina pectoris while causing minimum effects on the dynamics of cardiovascular circulation and on cardiac functions. It is a freely water soluble drug and is rapidly absorbed upon oral administration. In the solid crystalline state, nicorandil is stable under conditions of extreme dryness, but when it is exposed, although for short periods of time and room temperature, even at low humidity, a considerable humidity ensues. The progressive degradation of nicorandil entails the hydrolysis of inorganic ester contained in the molecule, with consequent liberation of nitric acid and N-(2-hydroxyethyl) nicotinamide, a compound that is not pharmacologically active at all considerable dosages, as evidenced by the substantial decrease in the content of active ingredient and therefore of the pharmacological activity. In the present study, *possibility of improvement in moisture stability of NRD,* a NNAE drug, has been investigated through formation of co-inclusion compounds in urea in presence of suitable RAE.

Preparation and characterization of urea co-inclusion compounds:

Urea co-inclusion compounds of all the NNAE drugs i.e. amiloride hydrochloride, enalapril maleate, glipizide, *cis*-retinoic acid and nicorandil were prepared using modification of the original Bengen's technique for preparation of urea inclusion compounds. Number of long straight chain compounds such as fatty acids, alkanes, alkenes, alcohols, amino acids, monoesters, and diesters can be employed as rapidly adductible endocyte. *However, dimerization of fatty acids in urea inclusion compounds leads to improved stability of the fatty acid-urea inclusion compounds adduct as compared to those of n-aliphatic compounds. Moreover, oleic acid is reported to increase bioavailability of hydrophobic drugs.* Hence, oleic acid was selected as the RAE for the purpose of co-inclusion of NNAE drugs in urea.

All the drugs and their co-inclusion compounds were characterized by following instrumental analysis:

- ★ FTIR spectroscopy: Characteristic peaks of urea (at 3436, 3333, 1629, 1150 and 1000 cm^{-1}) distinguishable from those of hexagonal urea (3420, 3225, occurrence of 4 bands between 1675-1590, 1160, 1011 and 791 cm^{-1})
- ★ DSC: Absence of melting endotherm of the endocyte and presence of two step incongruent melting endotherms of urea, which is a characteristic of the hexagonal complexed form of urea. Absence of melting endotherm for drugs in DSC thermograms of the urea co-inclusion compounds indicated that the drug may be present in amorphous form.
- ★ X-Ray diffraction: Difference in the interplanar spacings of tetragonal (3.97-4.04; 3.6-3.63 Å) and hexagonal (3.83-3.88; 3.93-3.41; 4.09-4.15; 7.08-7.19 Å) form of urea. Absence of peaks at characteristic spacings for the drugs in the diffractogram of the corresponding co-inclusion compound reveal that the drug is included in the hexagonal lattice formed by urea molecules and does not possess any lattice of its own.

Thus all the NNAE drugs were successfully included in parallel channels of urea lattice through the modified technique.

Thermal analysis of urea inclusion compounds:

Once the formation of urea co-inclusion compounds of NNAE drugs was confirmed, Modified Zimmerschied calorimetric method was used for estimation of minimum amount of RAE required for adduction of all the NNAE drugs selected for the present study. The procedure comprised of following two stages:

Stage I Determination of stoichiometric ratio between urea and endocyte, based upon measurement of temperature rise followed by addition of increments of RAE to methanolic solution of urea in the calorimeter.

The calorimetric method proposed by Zimmerschied *et al* for determination of composition of urea adduct was followed employing oleic acid as RAE in urea host.

Stage II. Determination of minimum ratio of RAE and drug for formation of co-inclusion compounds with urea.

A modified Zimmerschied calorimetric method was based on measurement of temperature rise following addition of increments of RAE to methanolic solution of urea containing excess of the drug. Hence, a methanolic solution of urea and NNAE drug was shaken in the calorimeter until equilibrium temperature was obtained. Increments of RAE were successively introduced into calorimeter. The calorimeter was stirred after each addition to facilitate attainment of equilibrium. The equilibrium temperature was then recorded after each successive addition. Increase in temperature on addition of successive increments of oleic acid to a methanolic solution of urea and NNAE was plotted. The curve demonstrated the following sequence of events i.e., an initial temperature rise, followed by intermediate final temperature, subsequent temperature rise and then achievement of a final temperature. Minimum amount of RAE required for adduction of NNAE in urea was calculated from the point of intersection of the lines of extrapolation of the initial rate of temperature rise and intermediate final temperature. Second stage of temperature rise was attributed to displacement of NNAE with RAE as evidenced by the fact that overall temperature rise is similar to that of RAE alone.

The said procedure was repeated for all the NNAE drugs selected for the present work and the minimum proportion of RAE required for the adduction of each of the NNAE drug was determined.

Urea-NNAE drug-RAE inclusion compounds containing varying proportions of the guests were prepared and their thermal behavior studied by DSC. Influence of relative proportion of RAE on the heat of decomposition was studied statistically. The regression analysis revealed good or excellent value of r^2 with reference to different NNAE. More the proportion of NNAE drug in the urea lattice, lesser will be the stability of the co-inclusion compound formed. Formation of urea inclusion compounds is exothermic in nature, which clearly indicates that the resulting compounds are stable. However, substituents in the guest moiety, which do not form part of a linear chain, will naturally lead to distortion and weakening of host structure comprising of narrow channels with consequent decrease in heat of decomposition of urea inclusion compounds. Thus, a*n increase in the proportion of RAE in the co-inclusion compound led to corresponding increase in heat of crystalline transition, which, in turn, is an indication of enhanced stability of the resulting co-inclusion compound.*

Mathematical models for prediction of heat of decomposition of urea inclusion compounds:

Correlation between the heat of decomposition of urea inclusion compounds containing aliphatic compounds and molecular descriptors was investigated. Values of *molecular connectivity index*, *Wiener's index* and *eccentric connectivity index* were computed for each of the 44 diverse aliphatic compounds comprising the dataset. Resulting data was analysed and suitable mathematical models were developed for prediction of heat of decomposition of urea inclusion compounds. Retrofit analysis of the models indicated that the model based on molecular connectivity index yielded the best statistical parameters and is indeed suitable for estimation of the heat of decomposition of urea inclusion compounds ($r \sim 0.94$). The results were internally cross-validated by leave-one-out procedure.

Influence of inclusion of drugs in urea on dissolution profile:

The dissolution profiles were investigated for all the pure drugs and their urea co-inclusion compounds containing varying proportions of NNAE and RAE. The dissolution profiles were evaluated by the dissolution efficiency (DE) parameter and the dissolved percentage (DP). The results obtained were as follows:

Amiloride Hydrochloride (AH): The extent of pure AH released was found to be quite low with $DP_{10} \sim 48$ % and DE_{10} 0.512. On the other hand, co-inclusion of drug in urea resulted in instantaneous and complete release of drug as exhibited by the enormous enhancement in DP_{10} and DE_{10} (96-98% and 0.91-0.93 respectively). These inclusion compounds were observed to exhibit much faster dissolution rates and complete dissolution of samples was achieved within 1 minute of addition of the contents to the dissolution medium.

Enalapril maleate (EM): The extent of pure enalapril maleate released was found to be comparatively low with dissolution of ~ 36 % of the contents in 5 min. On the other hand, co-inclusion of drug in urea provided instantaneous dissolution of ~ 100 % within 5 min. as exhibited by $DE_5 \sim 0.78$ for both the inclusion compounds.

Glipizide (GLP): The extent of pure drug released was found to be quite low exhibiting DE_{60} as low as 0.147. On the other hand, co-inclusion of drug in urea resulted in an

immediate and almost complete release of drug as exhibited by release of ~ 97% of contents within 2 min. However, this immediate release of drug contents was found to be followed by a subsequent decrease in drug contents in solution and DP_{60} was found to be as low as 44.5.

Cis-retinoic acid: The extent of pure *cis*-retinoic acid released was found to be quite low with DE_5 = 0% and DE_{60} ~0.03 due to hydrophobic nature of the drug. Co-inclusion of drug in urea provided a faster release of drug content as exhibited by DE_5 of ~ 0.64 for the two inclusion compounds containing varying proportions of drug and RAE. Co-inclusion of drug in urea resulted in an almost instantaneous release of drug as exhibited by release of ~ 94 % of contents within 2 min. However, this instantaneous release of drug contents in the dissolution medium was followed by a subsequent fall in amount of drug contents in solution and DE_{60} was found to be as low as ~ 0.219, though quite better than the same value for pure drug.

When urea inclusion compound containing NNAE as well as RAE as guest moieties comes in the contact with an aqueous dissolution medium, *the urea lattice dissolves almost instantaneously and results in immediate release of the included drug at a molecular level.* Also, inclusion of a NNAE drug along with RAE in urea leads to weakening/distortion of urea host lattice, manifested as subsequent decrease in the heat of decomposition of the resulting inclusion compound. The enhancement in the dissolution rate further indicates that inclusion compound formation could alter the solid state of drug. The same results were confirmed by dissolution profiles for urea co-inclusion compounds of Amiloride hydrochloride and enalapril maleate.

However, a somewhat different dissolution profile was obtained with urea co-inclusion compounds of Glipizide and *cis*-RA, which are both practically insoluble in water and hence belong to BCS class II. In these cases, the instantaneous and complete release of drugs from their corresponding co-inclusion compounds was observed to be followed by a subsequent decrease in drug contents in solution. *As both these drugs have limited aqueous solubility under the present dissolution conditions, the initially released drug molecules subsequently tend to crystallize in excess of solubility. This may be caused by non-sink conditions of the dissolution media. Since these drugs are rapidly permeable drugs, the released drug molecules may rapidly permeate through biological barriers in*

vivo and a built-up of concentration at the site of dissolution may not actually occur. Thus complete dissolution and subsequent permeation of these drugs can be expected in vivo.

Content uniformity:

The contents uniformity analysis for different urea co-inclusion compounds containing varying proportions of RAE: NNAE drug was carried out. From the experimental data, it was observed that mean drug content for different inclusion compounds was not significantly different. Therefore co-inclusion compounds of drug in urea lattice exhibit high content uniformity and hence can be exploited for the development of a quality formulation.

Influence of inclusion in urea on photostability:

Cis-retinoic acid is an unstable compounds, being sensitive to light, heat and oxygen. Theoretically, upon photo-exposure, the double bonds present in the conjugated polyene chain portion of the drug undergo isomerization to yield a photostationary mixture consists of a mixture of all possible geometric combinations including the original 13-*cis* form. Some of the effects of retinoic acid depend on the geometry of polyene chain. Hence, the development of novel formulations characterized reduced sensitivity towards retinoic acid photoisomerisation seems to be important. In the present study, an attempt was made to improve photostability of *cis*-retinoic acid through formation of urea co-inclusion compounds in presence of a suitable RAE. Photoexposure to simultaneous UV and visible light of *cis*-retinoic acid as well as its urea co-inclusion compounds was carried out in photostability chambers at 25°C and 60% RH, as per Q1B ICH guidelines for photostability testing. It was found that after irradiance with ~200W/m^2 of UV and ~750 Klux /hr of visible light exposure, ~ 72 % of the drug underwent photodecomposition. The same amount of photoexposure resulted in a residual drug concentration of ~ 35 % for urea co-inclusion compound of *cis*-retinoic acid. The experimental data obtained on photostability testing was subjected to various kinetic equations proposed for characterization of decomposition in solid state. The best fit for estimating kinetics of drug degradation both the drug sample and its urea co-inclusion

compound was obtained with unimolecular decay equation. While the decomposition rate constant for photodecomposition for pure drug was found to be 0.1698 day^{-1}. Co-inclusion of the drug in urea lattice led to a reduction in the value of reaction rate constant to the level of 0.1597 day^{-1}. The containment of guest moiety within urea hexagonal channels may tend to restrict the direct availability of incident photons (which provide necessary energy for its isomerization) to conjugated double bonds of *cis*-retinoic acid. Thus inclusion of drug in urea lattice reduces the photodegradation process when compared with that of the pure solid drug. Further improvement in photoprotection may be achieved by incorporation of increased relative proportion of RAE in the co-inclusion compound.

***Influence of inclusion in urea on moisture sensitivity*:**

Urea is stable under normal temperature and humidity conditions. However, urea is also known to be characterized by the critical relative humidity (RH_o) of 72.5 % at 30 °C. Pure urea, its inclusion complex with RAE alone (UOA), nicorandil and drug-RAE-urea co-inclusion compounds (NRDIC) were exposed to varying humidity conditions. It was observed that *inclusion compounds of urea, in which urea exists in its hexagonal form exhibit quite reduced moisture sorption as compared to that of the pure tetragonal form of urea.* Though inclusion complex formation led to increase moisture stability for urea, this does not seem to affect the critical relative humidity of urea as demonstrated by moisture uptake by UOA samples at humidity levels of ~74 %. Co-inclusion of nicorandil in urea complex along with oleic acid led to reduction in moisture stability of NRDIC (as compared to that of UOA). However, *the moisture uptake was found to decrease in the following sequence UOA< NRDIC < < tetragonal urea.*

In addition to above, inclusion of a moisture sensitive drug e.g. NRD in urea lattice was observed to *afford protection from atmospheric moisture content as exhibited by reduced degradation of nicorandil*, when co-included in urea lattice. HPLC analysis of nicorandil drug samples showed that pure drug, when stored in atmosphere of 60 % RH at 30 °C demonstrated ~ 75 % of the intact drug. Similar exposure of co-inclusion compounds NRDIC led to some reduction in the rate of degradation as manifested by 90 % of drug content left in the sample of co-inclusion compound.

Conclusion

Amiloride hydrochloride, enalapril maleate, glipizide, *cis*-retinoic acid and nicorandil- all substituted cyclic compounds which are not known to be adductible in urea under any known conditions were successfully included in urea through modified technique. Resulting products exhibited steep improvement in dissolution profile, excellent content uniformity and improved stability. Studies reveal that there is a vast potential for improvement of pharmaceutical characteristics of diverse nature for wide range of therapeutic agents through inclusion in urea. However, further studies are needed to exploit the full potential of urea as an adductor, which can be a promising alternative to cyclodextrins for improvement of pharmaceutical characteristics.

Each milestone says we have miles to go.....