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In-situ Solubilization of Class II Drugs During the Hydrosol-Gelation Phase in the Presence of Amphoteric Amino Acids, Polysaccharides, and Polymers: A Novel Approach in Controlled Release Drug Delivery.

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Introduction:

Inadequate aqueous solubility reflects a less favorable than desired free energy of transfer from solid phase to the aqueous solution and can be considered in two categories:

I. Those systems in which the intended solute is highly hydrophobic and does not hydrate sufficiently in water to provide the necessary free energy* to bring these molecules into solution.

II. Those systems which are highly polar and solvate well in water but are too tightly bound in their crystal lattices through ionic attraction and, more especially, hydrogen bonding forces to permit transfer to the aqueous phase.

* free energy may be increased via formation of polymorphs,solid solution,finely divided powders,formation of soluble complexes, and addition of specific additives to the system (in this work system could be a hydrophilic matrix).

The biopharmaceutical classification system(BCS) takes into account drug solubility and intestinal permeability of drug substances as described in table 1. According to the BCS rate and extent of drug absorption for immediate release products can be related to dissolution when highest dose strength is soluble in ≥; 250ml of media over the pH range of 1-7.5 and when extent of drug absorption across human intestinal membrane (not systemic BA) is ≥; 90% of an administered dose. With this in mind use of biorelevant media for IR products and prediction of *in-vivo* dissolution behavior has been adopted (*IVIVC*). It appears logical to consider extrapolating this general concept (BCS-IR) to modified release drug delivery systems too. Of course it should be recognized that the challenges and impact of solubility, permeability and delivery system transit time within entire GI tract becomes much more significant and complex with heterogeneity in pH, intestinal metabolism and permeability (Dressman et al 2001). As far as solubility is concerned it is especially feasible in the context of hydrophilic matrices to use and apply principles of colloid chemistry to induce solubilization, controlled hydration and micro environmental pH and formation of reversible complexation within various domains of the matrix during gelation and swelling phases.

Table 1.

• Guidance for Industry: FDA, 1995.
• Table compiled by R.Fassihi (2001).
• SR/CR= Only for drugs that qualify (in terms of PK/PD, solubility and permeability) for controlled release development.

Introduction: (Cont.)

Suggested Strategy for Solubilization of Poorly Soluble Drugs

- Determination of relevant solute properties
- Intrinsic solubility in water and media of various pH and composition.
- Usable pKa values, chemical structure,
- Octanol –water partition coefficient
- Selection of acceptable excipients and additives
- Select acceptable pH range,buffer components, surfactants ,co-solvents, complexing ligands, electrolytes, non-electrolytes, polymer(s) and their concentrations and viscosities.
- Solubilization
- Crystal modification, buffer, co-solvent (reduce the polarity of water), surfactants, micellization, reversible complexation via "salt in or Salt out" mechanisms, use of salts, particle size control etc.
- Co-solvents and surfactants + buffers
- Multiple co-solvents and surfactants including hydrotropy
- Facilitated hydrotropy (partially miscible aromatic solute + co-solvent can become a powerful solubilizing agent for drugs)

Purpose:

To evaluate the in-situ solubilization potential of isoleucine and glycine on nifedipine (Class II- Drug) within a novel hydrating matrix core. To optimize release kinetics of monolithic formulations for controlled and prolonged drug delivery of poorly soluble drugs.

Method:

Addition of specific additives for *in Situ* control of solubilization via "Salting in" or "Salting out" mechanisms

- Additives may either increase or decrease the solubility of a solute in a given system by interaction with the solute, solvent or components present.
- Additives that increase solubility are said to "Salt in" the solute and those that decrease solubility "Salt out" the solute and this can be expressed as follow:

» Log S/Sa = K Ca

- where ; S= solubility in the absence of additives;
- Sa= solubility in the presence of an additive;
- Ca= concentration of additives;
- K= the salting coefficient. If K is positive additive increases solubility and when negative it decreases the solubility. The influence of such additives on an insoluble drug are shown in Schematics 1 and 2.

Isoleucine has a non-polar tail $CH3CH2CH(CH3)$, as well as a polar end composed of $^+NH3CHCOO^-$, when appropriate ratio of lipophilic drug, isoleucine and selected additives are wet massed partial or total surface interaction / complexation is possible.

Schematic 1. Illustration of the complex formation by reversible association. Other amino acids and their physicochemical properties are shown in table 2.

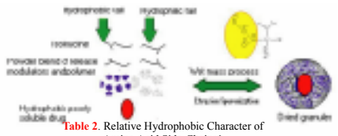
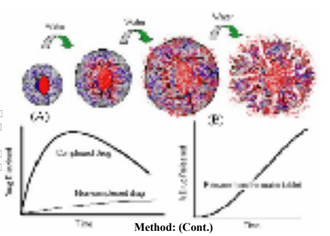


Table 2. Relative Hydrophobic Character of Amino Acid Side-Chains*

* High positive values indicate very hydrophobic amino acids, and negative values indicate amino acids with hydrophilic character. Glycine is considered as standard. (From V. Pliska et al. J. Chromatog. 216, 79, 1981).

Schematic 2: Representation of :(A), enhanced solubilization, oversaturation and finally higher dissolved level and (B), drug release from matrix tablet via "salt in" mechanism using the same granular composition in a hydrating matrix



Method: (Cont.)

Nifedipine (a model drug from BCS Class II); Isoleucine; Glycine, HPMC KM, PEO, Guar and release modulators were systematically wet massed in a planetary mixer in such a manner that slow hydrating and rapidly hydrating matrix components could be blended and compressed as shown in Figures 1 and 2.

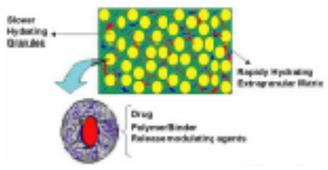
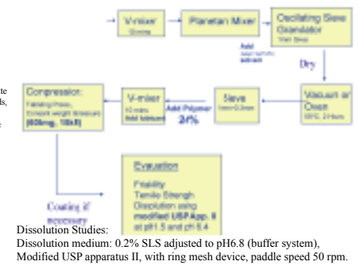


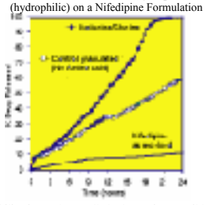
Figure 2. Preparation and Evaluation of Preliminary Formulations Via Wet Massing or Extrusion Spheronization

Insoluble Drug 40%
Amino Acid(s) 18%
Polymer(s) 18%



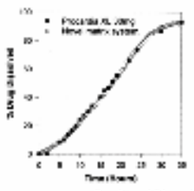
Dissolution Studies:
Dissolution medium: 0.2% SLS adjusted to pH6.8 (buffer system), Modified USP apparatus II, with ring mesh device, paddle speed 50 rpm.

Figure 3
Effect of a Combination of Isoleucine (hydrophobic) and Glycine (hydrophilic) on a Nifedipine Formulation



- Drug solubilization and controlled release via a possible Salt-in mechanism within a complex hydrophilic matrix

Figure 4.
Comparison of an Optimized Developed Novel Monolithic Uncoated Delivery System with Procardia XL "Push-Pull-OROS System"



- Dissolution medium: 0.2% SLS adjusted to pH6.8, USP apparatus 2, with ring mesh device, paddle speed 50 rpm.
- US Patent Allowed.

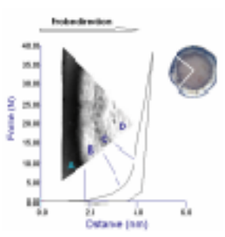
Results and Discussion:

Factors That Contribute to Matrix Hydration Dynamics, Boundary Translocation and Drug Release Include:

1. Polymer wetting, water transport and hydration rate
2. Polymer expansion ,chain relaxation and associated enthalpy changes
3. Effect of drug and other soluble or insoluble ingredients on the above through changes in:
   i. water availability
   ii. ionic strength
   iii. pH effect
   iv. interactions between different species (see table 2)
4. Differences in localized domains within the gel-network as a result of:
   i. non-uniform distribution of water and other ingredients
   ii. drug dissolution, release, pore collapse, entrapped air bubbles and presence of insoluble ingredients
5. General peripheral erosion and differential rates of swelling and erosion

The internal changes in the matrix can be evaluated and interpreted via textural analysis of the hydrating matrix core as shown in Figure 5.

Figure 5. Actual changes in gel layer and solid core boundary regions of a matrix tablet with time during the dissolution study



A. Fully hydrated region
B. Partially hydrated region
C. Infiltrated region
D. Glassy core

Typical force-distance profile (2 mm, round probe)and photomicrograph 3 hours after swelling (From Durig and Fassihi, J.Controlled Release (2002); vol. 80,pp45-56)

Results and Discussion:

Textural Analysis of A Hydrated Tablet

From the results shown complexation is possible when poorly soluble drug with a soluble material (amino acids & macromolecular carriers) interacts to form a soluble intermolecular complex. As most complexes are macromolecular as such are unable to cross lipid membranes and therefore it is essential that complex formation is reversible and free drug is released. Schematic 3 illustrates the dynamics and kinetics of solubilization within a hydrating matrix leading to liberation of free drug molecule via controlled system erosion,dissolution and diffusion mechanisms.Figure 6 demonstrate release profiles for an additional class 2 drug formulation based on the same principle.

Schematic 3.Dependence of Drug/Amino Acid Concentrations and Drug Release Rate on Matrix Composition and Swelling Kinetics

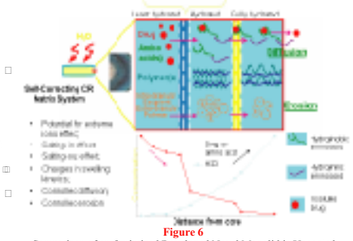
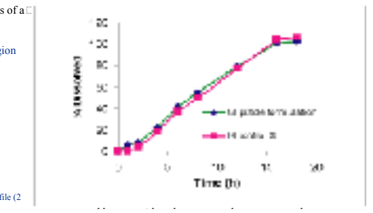


Figure 6
Comparison of an Optimized Developed Novel Monolithic Uncoated Delivery System for Glipizide with Glucotrol XL "Push-Pull-OROS System"



Results and Discussion:

Conclusion and Assessment:

In-situ solubilization of nifedipine or an insoluble drug occurs when drug and the combination of hydrophobic isoleucine and hydrophilic glycine were intimately granulated with a polymeric carriers of different viscosities.

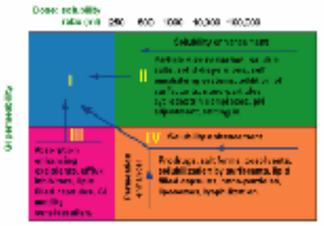
It appears that at appropriate stoichiometries in these formulations the hydrophobic nifedipine will interact with the hydrophobic tale of the isoleucine covered with hydrophilic glycine within polymers to form a soluble intermolecular complex.

Preferential interaction of amino acids and polymer carrier with water and hydration of composition surrounding the hydrophobic drug results in hydrating environment which tends to increase solubility and affect surface tension of water via "salting in" tendencies, resulting in gradual solubilization and controlled drug delivery by diffusion,and erosion.

Conclusion and Assessment (Cont.)

- Delivery system and approach has sound science behind it and has strong intellectual and scientific property position.
- Technology is anticipated to have favorable technical and regulatory success with commercialization potential.
- It uses conventional equipments for operation and proven materials that have acceptable financial and track record of good performance and have achieved proof-of-principle.
- Delivery system has the ability to deliver very high drug loads in near zero order fashion
- System has unique formulation and is competitively-superior to other technologies in drug delivery domain.
- The advent of BCS along with novel applications in solubilization within the swollen matrix demonstrated in this work may provide opportunity to enhance solubility of poorly soluble drugs by shifting Class II and IV toward Class 1 in terms of solubility behavior in order to extrapolate the BCS agenda to Modified release systems (see Schematic 4).

Schematic 4
Possibilities of shifting the solubility-dissolution characteristics from a very poorly soluble drug (D:S >250 ml) to D:S within the range of values encountered in the human GI tract



References

*Durig and Fassihi, J.Controlled Release (2002); vol. 80,pp45-56.
*Dressman et al. Pharm.Technology (2001); Vol.25, No.7,pp 68-76.
*Amino Acid Modulated Extended Release Dosage Form, US Patent Allowed.

Citation:

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