The Accordion Pill™, a gastro-retentive controlled release system– a new solution for key unmet needs

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ABSTRACT SUMMARY
A novel gastro-retentive (GR) delivery system, the Accordion pill™ (AP), was developed and tested in humans. The results show that the AP platform significantly improves the Pharmacokinetics (PK) of drugs with either narrow absorption window (NAW) or drugs with poor bioavailability due to limited aqueous solubility. Two cases are presented:
1. AP Carbidopa/Levodopa (AP-CD/LD) formulations have demonstrated superior PK, efficacy and safety in comparison to immediate and sustained release Levodopa and Dopa decarboxylase inhibitors (DDCI) formulations.
2. AP formulation of a Biopharmaceutics Classification System (BCS) class IV drug significantly increased the drug's bioavailability and overcame the drug's non-linear PK issue.

INTRODUCTION
Achieving efficient delivery of drugs that are characterized by NAW or poor bioavailability due to poor solubility is a key goal in the pharmaceutical industry for decades1. An innovative approach to address this task is by controlled release GR drug delivery systems. Retaining the dosage form in the stomach and releasing the drug in a controlled manner enables prolonged and continuous absorption phase of the drug in the upper parts of the gastrointestinal (GI) tract, resulting in improving the drugs’ known limited efficacy, safety profile and the need for frequent daily dosing. GR formulation can also enhance the absorption of poorly soluble drugs by increasing the apparent solubility in the stomach and GI tract, resulting in a consistent increase of the available drug amount at the site of absorption due to: a) Enhanced drug exposure to bile salts. b) Effective drug exposure to relatively larger volumes of stomach and GI media c) Increased solubility of drugs with pH-dependent solubility2.

The AP is a unique GR formulation composed of pharmaceutical (IIG listed) biodegradable polymeric films. It is a multi-layer, planar structure, folded to an accordion shape into a standard size capsule (Figure 1). Upon reaching the stomach, the capsule dissolves, the Accordion unfolds and is retained in the stomach for up to 12 hours, under regular calorie diets. While in the stomach, the accordion releases the drug in a controlled manner.

![Figure 1: Accordion pill general structure](image)

Two examples of drug enhancement by the AP drug delivery platform are presented:
a) NAW drug; Levodopa in AP formulations demonstrated significantly improved PK, efficacy and safety profile, in a phase II study in Parkinson's disease (PD) patients.
b) Poorly soluble drug; a BCS class IV drug in an AP formulation showed a significantly increased bioavailability in a Phase I PK study.

EXPERIMENTAL METHODS
AP formulations of Carbidopa/Levodopa were developed and evaluated in a phase II multi-center study in PD patients experiencing motor fluctuations. PK was tested in a multiple dose study in 8 patients following 6 days treatment at home, AP CD/LD 50/375 mg given BID vs. QID of commercial IR CD/LD 18.75/187.5mg. No LD medication was allowed for 10 hours before the first administration at day 7.

Efficacy and safety were tested in a 42-days study in 34 patients, taking AP CD/LD 50/375 mg (N=16) or 50/500 mg (N=18), vs. optimal immediate- and sustained-release DDCI/LD treatment.

APs containing a BCS class IV drug were formulated. The drug's current marketed formulation shows nonlinear PK, its solubility strongly decreases with increasing pH, and it is practically insoluble at pH 4.5 and higher. The formulation was tested in 12 healthy volunteers in a single-dose, three-way, crossover, comparative PK study with two doses of AP formulation (one AP and two APs) vs. the commercial formulation of the BCS class IV drug.

RESULTS AND DISCUSSION
AP formulation of a NAW drug- AP CD/LD demonstrated PK profile with significantly more stable LD levels (Figure 2). Peak-to-trough
fluctuations with the AP formulation were 50% lower as compared to the reference. LD's absorption phase was increased >6-fold. BID administration of AP CD/LD provided daily coverage of LD therapeutic plasma levels. LD's morning pre-dose plasma levels achieved by the AP CD/LD were significantly higher than those achieved with the IR formulation.

Patients treated with AP CD/LD formulations have demonstrated significantly less Total Off Time. The decrease in OFF time was greater with increasing dose (Figure 3). Good ON time (“ON time without dyskinesia” plus “ON time with non-troublesome dyskinesia”) also demonstrated an increased benefit with increasing dose. Patients treated with AP-CD/LD 50/500 mg had significantly less ON time with dyskinesias than patients taking the comparator regiment. The average number of LD doses was significantly reduced with the AP CD/LD treatment.

Figure 2: LD plasma levels in advanced PD patients following BID administration (8 hours apart) of AP-CD/LD 50/375 vs. QID administration (4 hours apart) of a commercial IR CD/LD formulation.

The AP formulation has demonstrated a significant prolongation of the absorption phase of the drug (Figure 4). The bioavailability of the drug was doubled in comparison to the commercial formulation. AUC and C_{max} achieved with one AP and two APs were proportional while the commercial formulation does not show PK dose proportionality in these dose ranges.

Figure 4: PK profile of two doses of AP formulation (one AP and two APs) vs. the commercial formulation of the drug.

CONCLUSION

The AP GR delivery system provides an efficient formulation solution for essential unmet needs, such as oral delivery of NAW and poorly soluble drugs.

The AP significantly improved the PK of LD (NAW drug), resulted in a major improvement of the drug's efficacy and safety profile. Chronic LD therapy is associated with motor complications often related to the drug's peripheral pharmacokinetics. LD's absorption is confined to the upper part of the GI tract and is characterized by a short clearance half-life.

Another AP formulation significantly improved the PK of a poorly soluble drug by breaching its nonlinear PK. The GR formulation overcame the solubility limiting absorption of the drug, leading to a major increase of the drug's bioavailability.

REFERENCES

2. Rong L, Water-insoluble drug formulation (2nd Ed.). 2008