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Amorphous Dispersion Development of ARRY-380, an ErbB2 Selective Inhibitor

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Abstract

Purpose

To develop and investigate the in vitro and in vivo behavior of amorphous dispersions of ARRY-380, an ErbB2 selective inhibitor.

Methods

Amorphous dispersions of ARRY-380 in PVP-VA, HPMC-P, HPMC-AS, CAP and Eudragit were prepared by solvent evaporation through spray drying from organic solvents. Physicochemical characterization of the spray dried dispersions (SDD's) as well as stability evaluations were completed using XRPD, mDSC, TGA, DVS, SEM and HPLC. In vitro dissolution testing was conducted on the SDD's to determine the degree of supersaturation they provided. In vivo investigation of ARRY-380 was evaluated in canines at 14 mg/kg, formulated as either a crystalline aqueous suspension or as an amorphous dispersion (3:7 ARRY-380/PVP-VA SDD in H2O). The potential effect of gastric pH and formulation on the systemic exposure of ARRY-380 was assessed by administering pentagastrin (to increase gastric acid production) and famotidine (to inhibit gastric acid production) prior to administration of both ARRY-380 formulations. Plasma samples were collected as a function of time and analyzed for ARRY-380 concentration.

Results

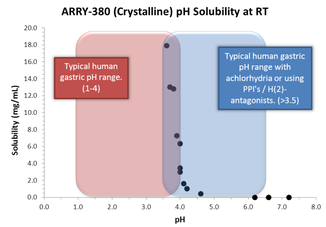
Physicochemical characterization by XRPD and mDSC confirmed that that all of the SDD's were amorphous. TGA showed the SDD's contained less than 1% THF, and DVS analysis revealed that the dispersions were moderately hygroscopic. Dissolution testing at pH 6.5 was found to show that the degree of supersaturation was ranked as PVP-VA >HPMCP> Eudragit> HPMC-AS > CAP from highest to lowest. Stability analysis at 40° C/75 %RH revealed that ARRY-380 was only stable in the PVP-VA SDD. The canine PK study showed that crystalline ARRY-380 exhibited pronounced changes in exposure (AUC and C_{max}) when animals were pretreated with pentagastrin versus famotidine whereas the PVP-VA SDD showed little to no change.

Conclusion

The data suggests ARRY-380 can be formulated as an amorphous dispersion with PVP-VA and that the dissolution of the SDD will be superior at elevated pH. The in vitro performance of the SDD was confirmed by in vivo testing where the SDD provided increased exposure at elevated gastric pH.

Purpose

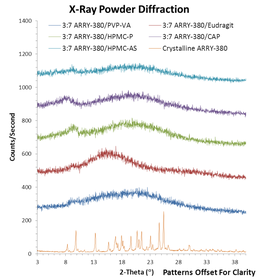
- ARRY-380 is an orally bioavailable inhibitor of the human epidermal growth factor receptor tyrosine kinase ErbB-2 (also called HER2). ErbB-2 is overexpressed in a variety of cancers and plays an important role in cellular proliferation and differentiation.
- ARRY-380 is a highly permeable, weak base that exhibits a pH dependent solubility profile (as shown on the right) and contains acidity constants (pKa) at 2.3, 4.3 and 6.3.
- Clinical dosing in oncology patients was found to show high variability in AUC/C_{max}, on the order of 80%, in which solubility, dissolution and gastric pH were possible implications.
- The present study was undertaken to develop and investigate the in vitro and in vivo behavior of amorphous dispersions of ARRY-380 and to probe the exposure and/or variability in AUC and C_{max} at elevated pH.

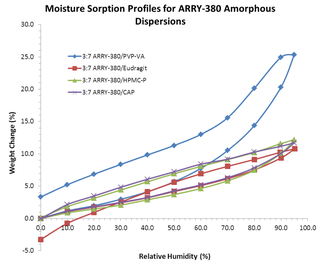


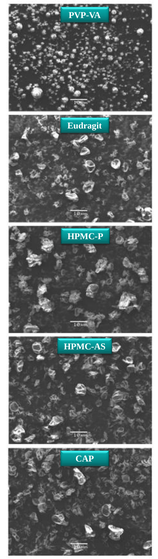
Methods

- SDD's were prepared at a 30% drug load by spray drying using a Büchi B290 from 1:3 Methanol (MeOH):Tetrahydrofuran (THF). The collected SDD's were secondary dried under vacuum at 40 °C for approximately 24 hours.
- A Rigaku Ultima III diffractometer with a Cu radiation source (44 kW, 40 mA) was used to collect X-ray powder diffraction (XRPD) patterns at ambient temperature and pressure from 3 to 40 °2θ.
- Thermal analysis was completed using a TA Instruments Q1000 DSC using aluminum pin-hole pans at 2 °C/min (modulated at +/- 1.27 °C every 60 seconds) under N_2 and a TA Instruments Q50 TGA at 10 °C/min under N_2.
- Hygroscopicity profiles were generated isothermally at 25 °C using a Hiden IGAsorp moisture sorption analyzer.
- Electron micrographs were acquired using a Joel JSM6480LV scanning electron microscope with a secondary electron scattering detector at 10 kV. Samples were prepared on aluminum stubs containing conductive carbon tape.
- Dissolution analysis was completed in phosphate buffer at pH 6.5. Samples were collected and analyzed by HPLC.
- Stability of the SDD's was investigated at 40 °C/75 %RH in open vials. Samples were analyzed for purity using HPLC.
- An in vivo pharmacokinetic study was completed in fasted, male beagle dogs at 14 mg/kg with n=4 dogs per group. Pentagastrin (6 µg/kg, IM) or Famotidine (40 mg, PO) was administered to the dogs prior to dosing to control the gastric pH of the dogs. Plasma was analyzed by LC-MS/MS and PK parameters were calculated using Phoenix WinNonlin®.

Characterization of Amorphous Dispersions







- XRPD analysis was found to show that each of the materials was amorphous and that no detectable crystalline ARRY-380 was present.
- Moisture sorption analysis showed that the PVP-VA dispersion was the most hygroscopic with 14 % weight gain at 80 %RH. The Eudragit, HPMC-P and CAP dispersions all showed similar profiles with approximately 7.5 % weight gain at 80% RH.
- In addition to PVP-VA being the most hygroscopic, it also showed the highest degree of hysteresis.
- No crystallization of ARRY-380 was observed after desorption in any of the dispersions.

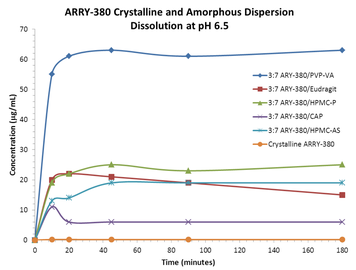
Polymer Type	API:Polymer	Tg (°C)	Wt. Loss by TGA (%)	% THF (w/w)	Physical Form	Hygroscopicity (% Wt. Change at 80% RH)
PVP-VA	3:7	117	2.3	0.5	Amorphous	14.4
Eudragit L100	3:7	116	5.9	4.5	Amorphous	7.5
HPMCP-H55	3:7	149	1.7	0.3	Amorphous	7.5
HPMC-AS (M)	3:7	113	NA	NA	Amorphous	NA
CAP	3:7	179	1.9	0.5	Amorphous	7.8

- The glass transition temperature (T_g) was measured for each dispersion and was found to show that each SDD had a relatively high T_g above 110 °C.
- Residual solvent analysis showed that all of the dispersions, except Eudragit, had less than 0.5 % THF and no detectable MeOH.
- SEM Analysis shows that morphology of the PVP-VA dispersion was spherical.
- The Eudragit, HPMC-P, HPMC-AS and CAP dispersions all showed collapsed, spherical shaped particles.

In Vitro Dissolution Testing of Amorphous Dispersions

- Dissolution analysis of the ARRY-380 amorphous dispersions, under non-sink conditions, was completed to investigate the degree of supersaturation the amorphous dispersions provided over that of the crystalline API at elevated pH.
- The amorphous dispersions were found to dramatically increase the solubility and dissolution rate of ARRY-380 over crystalline API, in addition the dispersions were found to maintain the supersaturation over a period of 180 minutes.
- The degree of supersaturation was ranked as PVP-VA >HPMCP> Eudragit> HPMC-AS > CAP from highest to lowest.

Sample	Maximum Conc. (µg/mL)	AUC (µg/mL*hr)
Crystalline	0.2	NA
3:7 ARRY-380/PVP-VA	63	245
3:7 ARRY-380/Eudragit	23	71
3:7 ARRY-380/HPMC-P	25	97
3:7 ARRY-380/HPMC-AS	19	68
3:7 ARRY-380/CAP	11	37



Stability Screen of Amorphous Dispersions

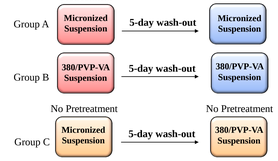
- A stability screen of the PVP-VA, Eudragit, HPMC-P and CAP spray dried dispersions was completed at 40 °C/75% RH under open conditions, in glass vials, over a period of 8-days.

Time	HPLC Area %			
	3:7 ARRY-380/PVP-VA	3:7 ARRY-380/Eudragit	3:7 ARRY-380/HPMC-P	3:7 ARRY-380/CAP
Standard	99.39	99.39	99.39	99.39
As received	99.45	98.63	97.30	95.45
4-days	99.21	96.10	93.03	90.89
8-days	99.35	93.16	86.63	87.15

- HPLC analysis for ARRY-380 purity was found to show that the Eudragit, HPMC-P and CAP dispersions were unstable under accelerated conditions. The main degradant observed was a hydrolysis product, likely due to the acidic nature of these polymers. The ARRY-380/PVP-VA dispersion was the only SDD found to be stable.
- XRPD analysis over the course of the study showed no evidence of crystallization for any dispersion.

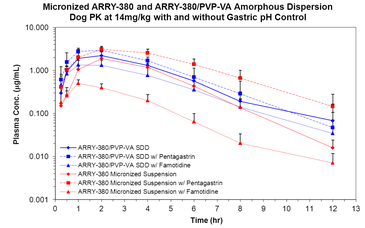
In Vivo Pharmacokinetics of ARRY-380 in Canines

- Based upon the dissolution, physicochemical properties and stability data the 3:7 ARRY-380/PVP-VA amorphous dispersion was selected for further investigation.
- The PVP-VA dispersion was tested against crystalline, micronized (d(v, 0.9) = 3.0 µm) suspension formulation under normal fasted conditions as well as with pretreatment using Pentagastrin or Famotidine. To reduce variability, dogs were crossed over from pentagastrin to famotidine after a 5-day washout period.



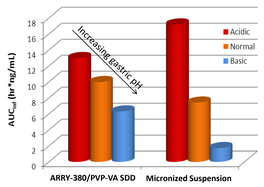
pH Modifier	Gastric pH*
Pentagastrin	2 - 3
Famotidine	5 - 7.5

*R. Zhou, et. al. *Pharm. Res.*, *Vol. 22, No. 2, Feb. 2005*



Pretreatment	Dosing Formulation	AUC_{inf} (µg*hr/mL)	C_{max} (µg/mL)
None	Micronized ARRY-380 Suspension	7.43 ± *1.77*	1.88 ± *0.35*
	3:7 ARRY-380/PVP Sprayed Dried Dispersion	10.0 ± *2.7*	2.29 ± *0.54*
6 µg/kg Pentagastrin	Micronized ARRY-380 Suspension	17.2 ± *2.7*	3.29 ± *0.13*
	3:7 ARRY-380/PVP Sprayed Dried Dispersion	13.0 ± *3.6*	3.12 ± *0.62*
40 mg/dog Famotidine	Micronized ARRY-380 Suspension	1.74 ± *0.39*	0.514 ± *0.092*
	3:7 ARRY-380/PVP Sprayed Dried Dispersion	6.32 ± *2.88*	1.45 ± *0.54*

AUC_{inf} and C_{max} are shown as Geometric Mean ± *CV*



- Comparing the non-pretreated dog data reveals that the overall exposure (AUC) was not increased by the ARRY-380/PVP-VA amorphous dispersion versus the crystalline API and that the variability was similar as well.
- Analysis of the exposure as a function of gastric pH shows that the micronized ARRY-380 exhibits much greater pH dependence than the PVP-VA amorphous dispersion. This is evidenced by the large difference in AUC observed between the pentagastrin versus famotidine treated groups where the micronized API showed approximately a 10x difference and the PVP-VA dispersion only showed ~2x difference.

Conclusions

- The data suggests ARRY-380 can be formulated as an amorphous dispersion with PVP-VA and that the dissolution of the SDD will be superior at elevated pH. The in vitro performance of the SDD was confirmed by in vivo testing where the SDD provide increased exposure at elevated gastric pH.
- The study indicates that the exposure and variability in oncology patients, that exhibit a wide range in gastric pH, could be enhanced through use of an amorphous dispersion.