Formulation development of the DuoGel: a dual chamber vaginal/rectal anti-HIV microbicide gel

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ABSTRACT

Purpose: The DuoGel, an anti-HIV gel microbicide formulation containing IQP-0528, is currently being developed as a single product for both safe vaginal and rectal administration to address the increasing evidence of both vaginal and anal intercourse in the same sexual act by reducing complexity of maintaining separate dosage forms.

Methods: The DuoGels with IQP-0528 were formulated from GRAS excipients approved for both vaginal and rectal administration (hydroxyethyl cellulose, glycerin, methyl/propyl paraben, and carbomer) and evaluated from physicochemical and biological properties. First, the pH and osmolality of the DuoGels were defined by a target product profile. DuoGel viscosity was measured under parallel plate geometry from 1E-5 to 200 s^{-1}. *In vitro* drug release was performed in Franz cells through a cellulose membrane over 6 hours. The rheological spreading and distribution of 4 mL of DuoGel was evaluated for 2 hours under 1.143 lbf. *In vitro* toxicity of the DuoGels was performed against CaSki, HEC1A, and ME180 cell lines and Lactobacilli for 24 hours. *In vitro* efficacy was performed in PBMC against HIV-1 infection for 7 days. The *ex vivo* toxicity, permeability, and efficacy of the DuoGels were performed in both polarized explant ectocervical and colorectal tissues.

Results: Beginning from a developed "vaginal only" gel formulation, the DuoGel formulation was developed and manufactured first to a specific pH (6.00) and osmolality (300 mmol/kg) to accommodate rectal administration. The identified DuoGel formulation displayed no *in vitro* cellular or bacterial toxicity at 1000 µg/mL (highest concentration). It also displayed no loss in viability in both explant ectocervical and colorectal tissue. The DuoGel formulation, with a viscosity of 59.44 ± 5.48 Pa*s at 1 s^{-1}, resulted in a gel distribution of 103.2 cm^2 (70.5% of the universal placebo gel spreading). The DuoGel produced an *in vitro* and *ex vivo* drug release rate of 23 ± 3 µg/cm^2 hr to prevent HIV-1 infection in both vaginal and rectal environments with an EC_{50} value of 2.34 ± 0.49 ng/mL.

Conclusions: This study has identified a gel formulation that has the potential to safely prevent HIV-1 infection in two different environments: vagina and rectum.

METHODS

Formulation: The DuoGels with IQP-0528 were formulated from GRAS excipients approved for both vaginal and rectal administration (hydroxyethyl cellulose, glycerin, methyl/propyl paraben, and carbomer) and evaluated from physicochemical and biological properties. First, the pH and osmolality of the DuoGels were defined by a target product profile. DuoGel viscosity was measured under parallel plate geometry from 1E-5 to 200 s^{-1}. *In vitro* drug release was performed in Franz cells through a cellulose membrane over 6 hours. The rheological spreading and distribution of 4 mL of DuoGel was evaluated for 2 hours under 1.143 lbf.

***In vitro* evaluations:** *In vitro* toxicity of the DuoGels was performed against CaSki, HEC1A, and ME180 cell lines and Lactobacilli for 24 hours. *In vitro* efficacy was performed in PBMC and TZM-bl against HIV-1 infection for 7 days.

Explant evaluations: The *ex vivo* toxicity and efficacy of the DuoGels were performed in both polarized explant ectocervical and colorectal tissues. For toxicity evaluations, the biopsied tissue was set in a polarized transwell system and the DuoGel formulation applied for 24 hour culture. Tissue viability was determined via histological analysis (H&E staining). Efficacy was similarly evaluated in the polarized transwell system. Efficacy was evaluated over a 21 day culture with HIV replication being monitored via p24 immunohistochemistry.

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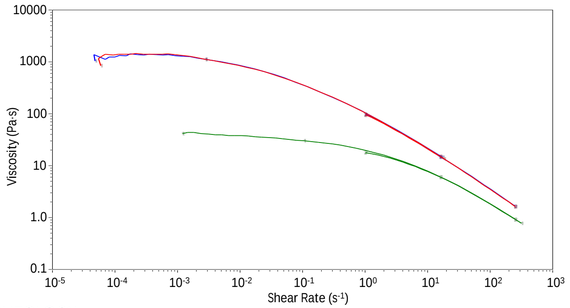
RESULTS

DuoGel Formulations (% w/w)							
FID	HEC	Glycerol	Methyl Paraben	Propyl Paraben	Carbopol	Phosphate Buffer	IQP-0528
3000	2.25	2.50	0.20	0.05	0.25	qs 100	1.00
3001	2.50	2.50	0.20	0.05	0.00	qs 100	1.00
3002	2.10	2.50	0.25	0.05	0.25	qs 100	1.00

DuoGel Characteristics					
FID	Appearance	pH	Osmolality (mmol/kg)	Permeability Rate* (µg/cm^2hr)	Spreadability**
3000	White cream	5.94	271 ± 40	6.07 ± 1.11	0.63
3001	White cream	5.76	256 ± 33	22.75 ± 8.44	1.02
3002	White cream	6.08	260 ± 36	23.03 ± 2.85	0.64

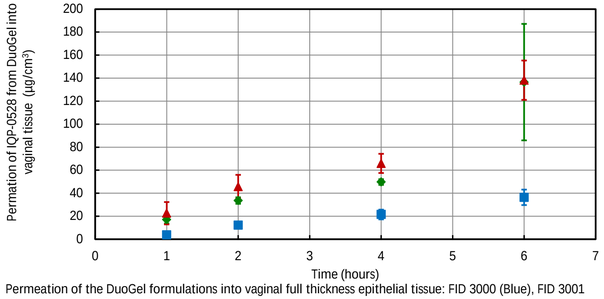
* Into *in vitro* vaginal epithelial tissue

** Compared to Universal placebo gel

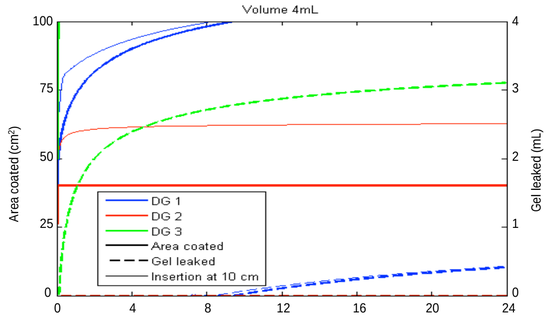


RHEOLOGY: Viscosity of the DuoGel formulations: FID 3000 (Blue), FID 3001 (Green), and FID 3002 (Red). The gel formulations were evaluated under both a sheer stress sweep and a shear rate sweep.

DRUG DELIVERY:



Permeation of the DuoGel formulations into vaginal full thickness epithelial tissue: FID 3000 (Blue), FID 3001 (Green), and FID 3002 (Red). The gels were added to the tissue for 6 hours at 37˚C.



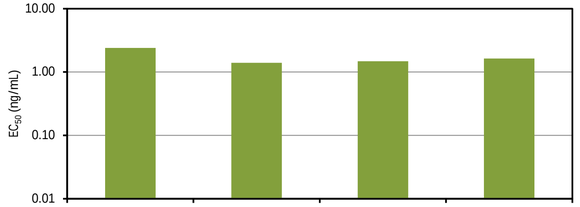
Spreading of three different DuoGel formulations: DG1 (blue – gel viscosity of 71 Pa·s at 1 s^{-1} shear rate), DG2 (red – gel viscosity of 178 Pa·s at 1 s^{-1} shear rate), and DG3 (green – gel viscosity of 8 Pa·s at 1 s^{-1} shear rate). Four milliliters of the gel was inserted mid-vagina (10 cm) and the area covered by the gel (solid line) vs. volume of gel that leaked (dashed line) was evaluated for 24 hours.

FORMULATION STABILITY

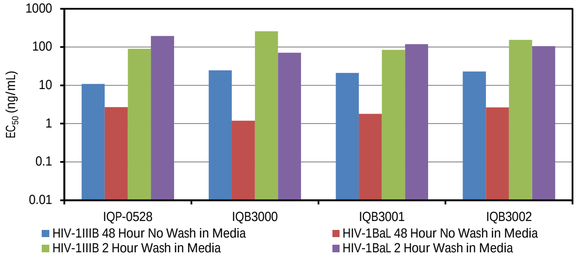
FID	40˚C / 75% R.H.	0 months	1 month	3 months
3000	Osmolality (mmol/kg)	271 ± 40	229 ± 23	401 ± 24
	pH	5.94	5.96	5.98
	% IQP-0528 (w/w)	0.957 ± 0.000	0.957 ± 0.003	1.016 ± 0.006
	Viscosity @ 1/s (Pa·s)	105.01 ± 2.48	103.75 ± 2.64	98.82 ± 0.85
3001	Osmolality (mmol/kg)	256 ± 33	233 ± 0	404 ± 27
	pH	5.76	5.54	5.77
	% IQP-0528 (w/w)	1.072 ± 0.002	1.016 ± 0.002	0.955 ± 0.002
	Viscosity @ 1/s (Pa·s)	43.77 ± 1.56	29.95 ± 0.44	18.29 ± 0.67
3002	Osmolality (mmol/kg)	260 ± 36	245 ± 19	369 ± 35
	pH	6.08	5.84	6.04
	% IQP-0528 (w/w)	0.981 ± 0.004	1.007 ± 0.006	0.928 ± 0.001
	Viscosity @ 1/s (Pa·s)	89.79 ± 5.97	99.74 ± 1.82	97.24 ± 2.06

IN VITRO TOXICITY AND EFFICACY:

- No toxicity observed to Ca-Ski, ME180 or HEC1A cells after 24 hours of exposure up to a concentration of 1 mg/mL.
- No toxicity to *Lactobacillus* after 24 hours of exposure up to a concentration of 1 mg/mL.
- No toxicity to epivaginal tissue after 24 hours of exposure up to a concentration of 1 mg/mL.

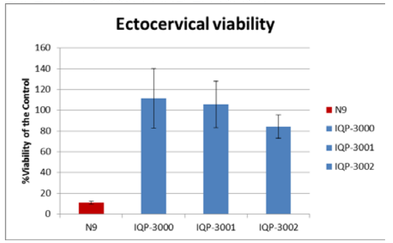


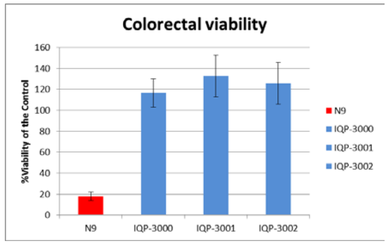
In vitro efficacy of the DuoGel formulations against HIV-1_{IIIB} and HIV-1_{BaL} in Human PBMCs. The effective concentration to inhibit 50% infection (EC_{50}) was evaluated for unformulated IQP-0528, FID3000, FID3001, and FID3002

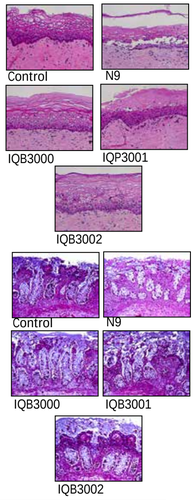


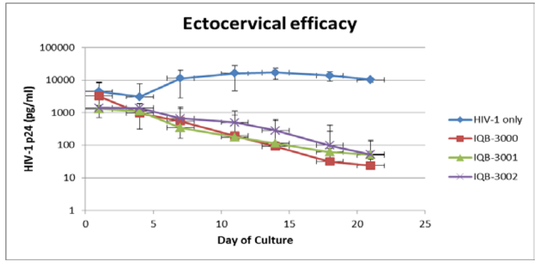
In vitro efficacy of the DuoGel formulations against HIV-1_{IIIB} and HIV-1_{BaL} in TZM-bl-FcRI Cells. The effective concentration to inhibit 50% infection (EC_{50}) was evaluated for unformulated IQP-0528, FID3000, FID3001, and FID3002.

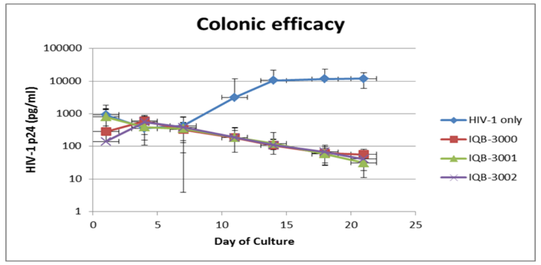
EXPLANT TOXICITY AND EFFICACY:











CONCLUSION

DuoGel formulation FID3002 was identified as the lead formulation for the vaginal/rectal microbicide gel due to its defined target product profile and *in vitro* and *ex vivo* activity.