CERSI
UCSF-Stanford

Formulation and Process Development of Harvoni

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Agenda/Outline

List of abbreviations

Case Study: Harvoni® Formulation and Process Development

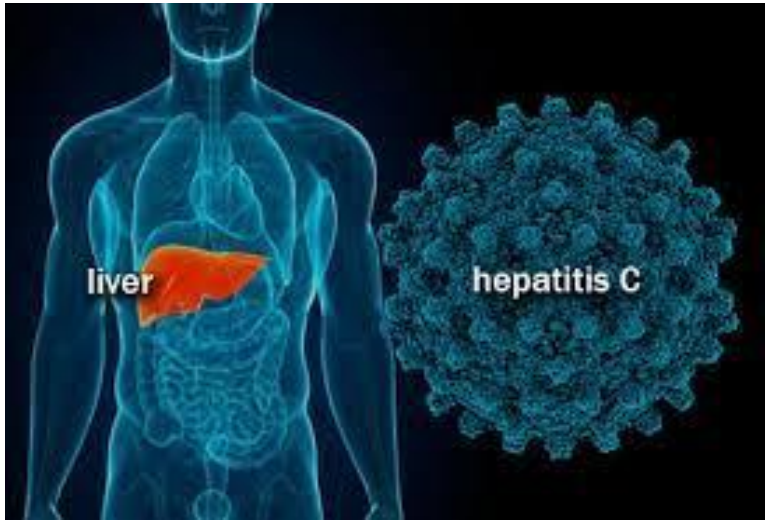
- Overview of Hepatitis C and standard of care for HCV in 2013
- Development of ledipasvir (LDV) tablet, an NS5A inhibitor
- Overcoming BCS Class II biopharmaceutical properties of LDV
- Development of a single tablet regimen (STR) containing LDV and sofosbuvir

List of abbreviations

API = active pharmaceutical ingredient
ARA = acid reducing agent
FaSSIF = fasted state simulated intestinal fluid
FDC = fixed-dose combination
FeSSIF = fed state simulated intestinal fluid
GMP = good manufacturing practices
GT = genotype
HCV = hepatitis C virus
IFN = interferon
IR = immediate release
LDV = ledipasvir (aka GS-5885)
PEG or PegIFN = pegylated interferon
PI = protease inhibitor
RBV = ribavirin
SDD = spray-dried dispersion
SGF = simulated gastric fluid
SOF = sofosbuvir
STR = single tablet regimen
SVR = sustained virologic response
TPP = target product profile

Hepatitis C is an inflammation of the liver caused by the hepatitis C virus (HCV)

- Discovered in **1989**[1].
- Transmission of HCV is **bloodborne**
  - Most infection occurs through exposure to contaminated needles or syringes, unsafe health care, unscreened blood transfusions, injection drug use and sexual practices that lead to exposure to blood.
- The virus can cause both **acute and chronic** hepatitis [2,3]:
  - **Acute HCV infection** : usually asymptomatic and most do not lead to a life-threatening disease. Around 30% (15–45%) of infected persons spontaneously clear the virus within 6 months of infection without any treatment .
  - 85% patients cannot clear the virus and progress to **chronic HCV infection**.
    - The severe results of chronic infection are [4] :
      - **cirrhosis**
      - **hepatocellular cancer**
      - **liver transplantation**
      - liver-related **death** worldwide



https://kauveryhospital.com/blog/gastroenterology/what-causes-hepatitis-c/

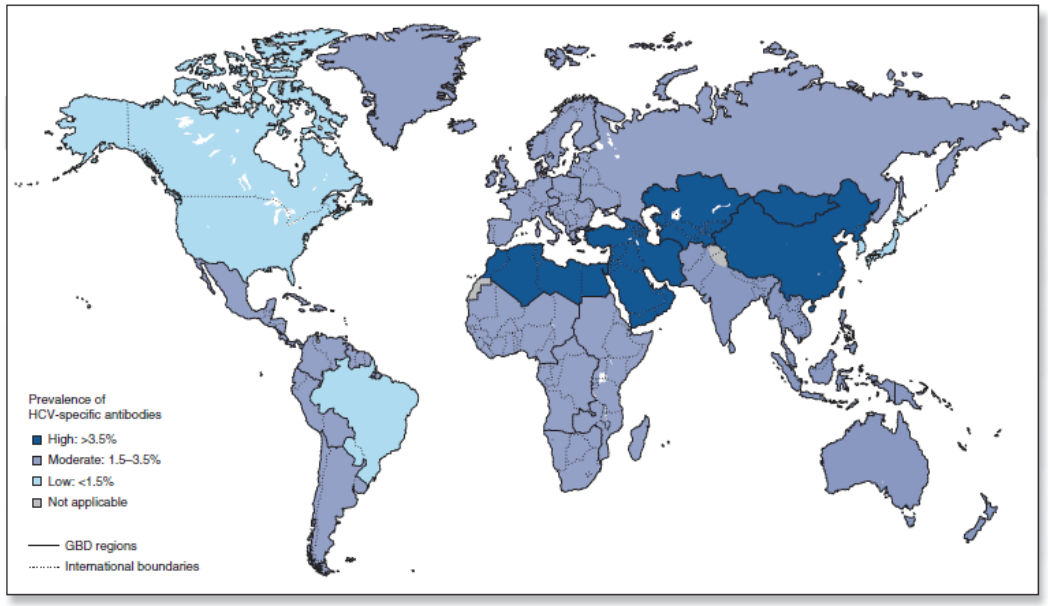
1. Lancet, VOLUME 385, ISSUE 9973, P1124-1135, MARCH 21, 2015
2. Lancet, Vol 385, Volume 385, Issue 9973, 21–27 March 2015, Page 1045
3. https://www.who.int/news-room/fact-sheets/detail/hepatitis-c
4. Lancet Gastroenterol Hepatol, 2017; 2: 161–76

In 2013, HCV infection was an unmet medical need[1,2]

In 2013, chronic HCV infection was a **global health problem**[1, 2]:

- 3% (170 million) of the world' population were infected by HCV
- From 1994 - 2015, the annual death from HCV had quadrupled
- HCV infection ultimately causing around 350,000 deaths/year[3]
  - 27% of cases of cirrhosis world-wide were attributed to HCV infection
  - 25% of hepatocellular carcinoma cases were attributed to HCV infection

Hepatitis C global prevalence 2013 (%)[4]

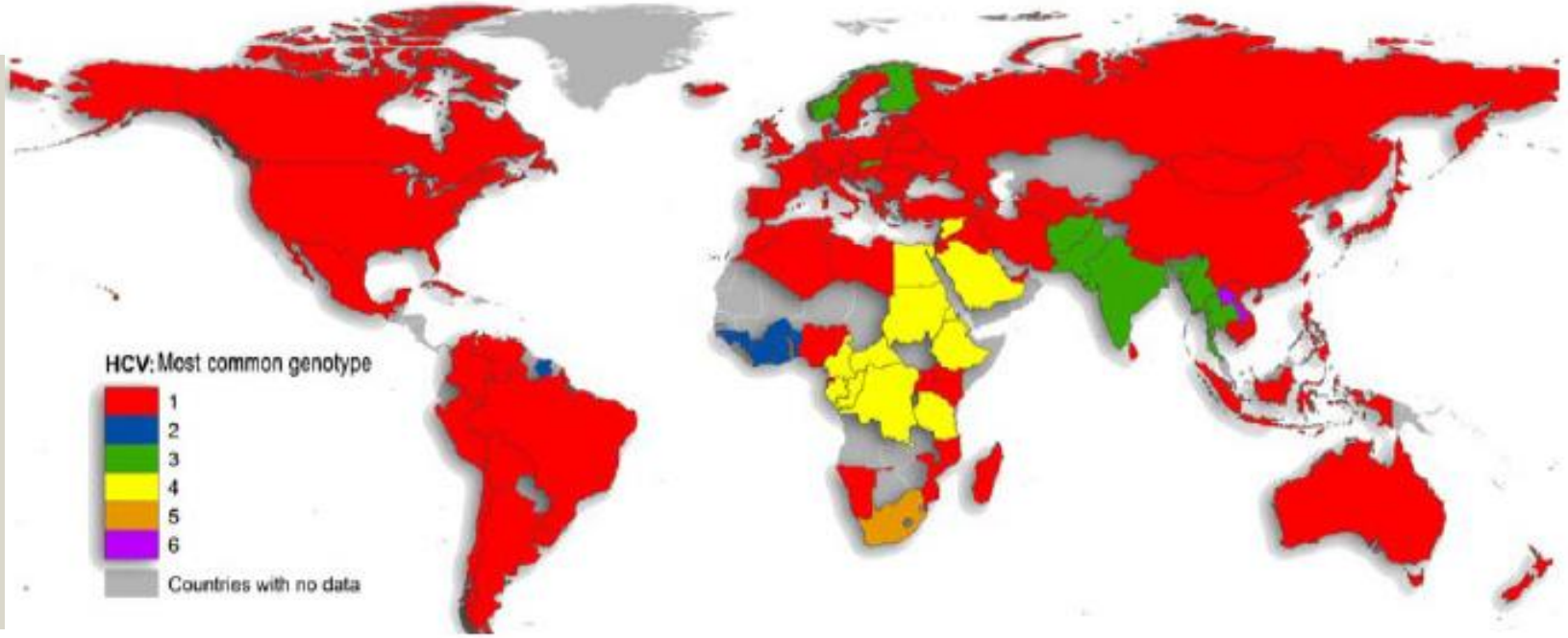


1. *Lancet,* Vol 385, Volume 385, Issue 9973, 21–27 March 2015, Page 1045
2. *Lancet,* Vol 385, Volume 385, Issue 9973, 21–27 March 2015, Page 1045
3. Zaltron S., *BMC Infect Dis.,* 2012; 12 (suppl 2): S2
4. *Nature Medicine* volume 19, pages 850–858 (2013)

HCV has 6 major genotypes (GT) and GT1 is the most prevalent worldwide

- **GT1** (40%-50% of all HCV infections)
  - subtype 1a : 31%
  - subtype 1b : 68%
- **GT2** (~10%)
- **GT3** (~30%)
- **GT4** (~10%)
- **GT5** (~<1%)
- **GT6** (~5%)

Countries by Majority Genotype[1]



1 Messina J et al. *Hepatology*. 2015;61:77–87

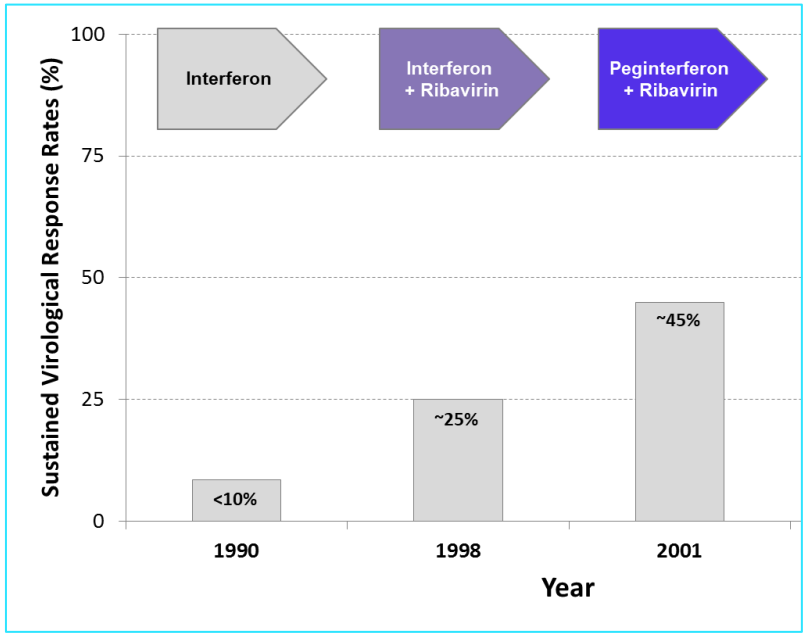
Evolution of HCV treatment

For many years treatment for HCV was inadequate

Standard of care until 2011 was a combination of SC pegylated interferon alpha (180 µg QW) and oral ribavirin tablets (800 -1200 mg QD depending on genotypes)[1, 2]

- This combination could lead to an SVR
- Success rates of ~ 45% depending on genotype
- Long and cumbersome treatment depending on genotype
- Treatment is associated with significant adverse events
- Poorly tolerated
- Less efficacious in patients with advanced disease
- Significant number of patients ineligible for interferon therapy

Changes in Standard of Care for HCV and Improvements in Numbers of Sustained Virological Reponses (SVR*) [1]



- SVR means that HCV virus is not detected in the blood ≥ 12 weeks after completing treatment.
- SVR is regarded as a cure, although it does not prevent future reinfection

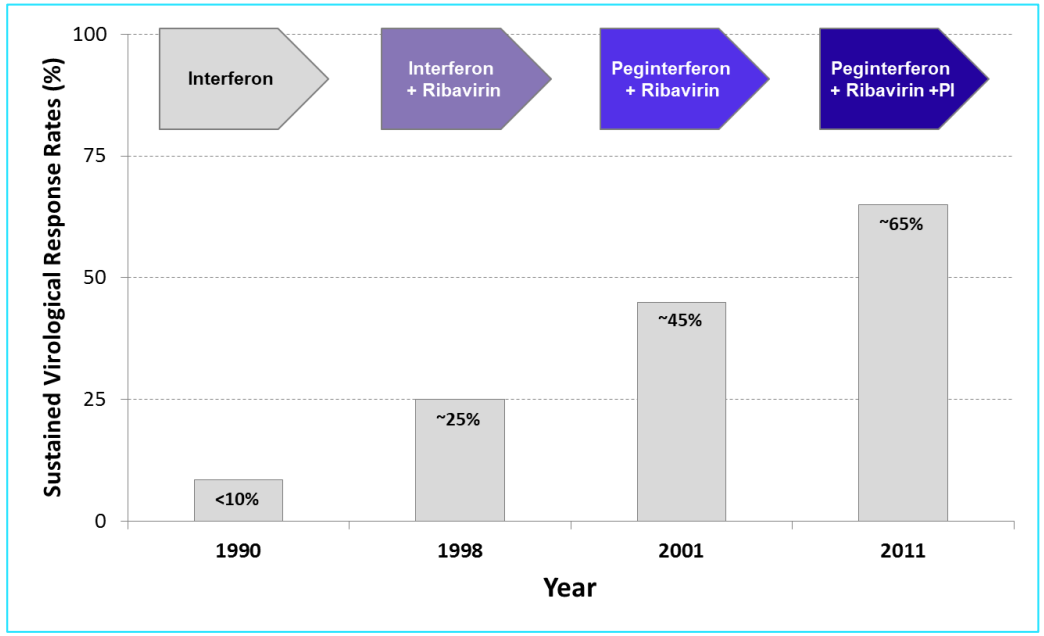
1. *Lancet*, VOLUME 385, ISSUE 9973, P1124-1135, MARCH 21, 2015
2. Fried MW et al., *N Engl J Med* 2002; 347: 975–82

Evolution of HCV treatment

Late 2011 : Triple combination PEG/RBV combined with TID dosing of a protease inhibitor (telaprevir or boceprevir)

- Complexity of protease inhibitor response guided therapy
- Increased toxicities including rash (telaprevir) or grade 3 or 4 anemia.
- SVR ~ 65%

Changes in Standard of Care for HCV and Improvements in Numbers of Sustained Virological Reponses (SVR*) [1]



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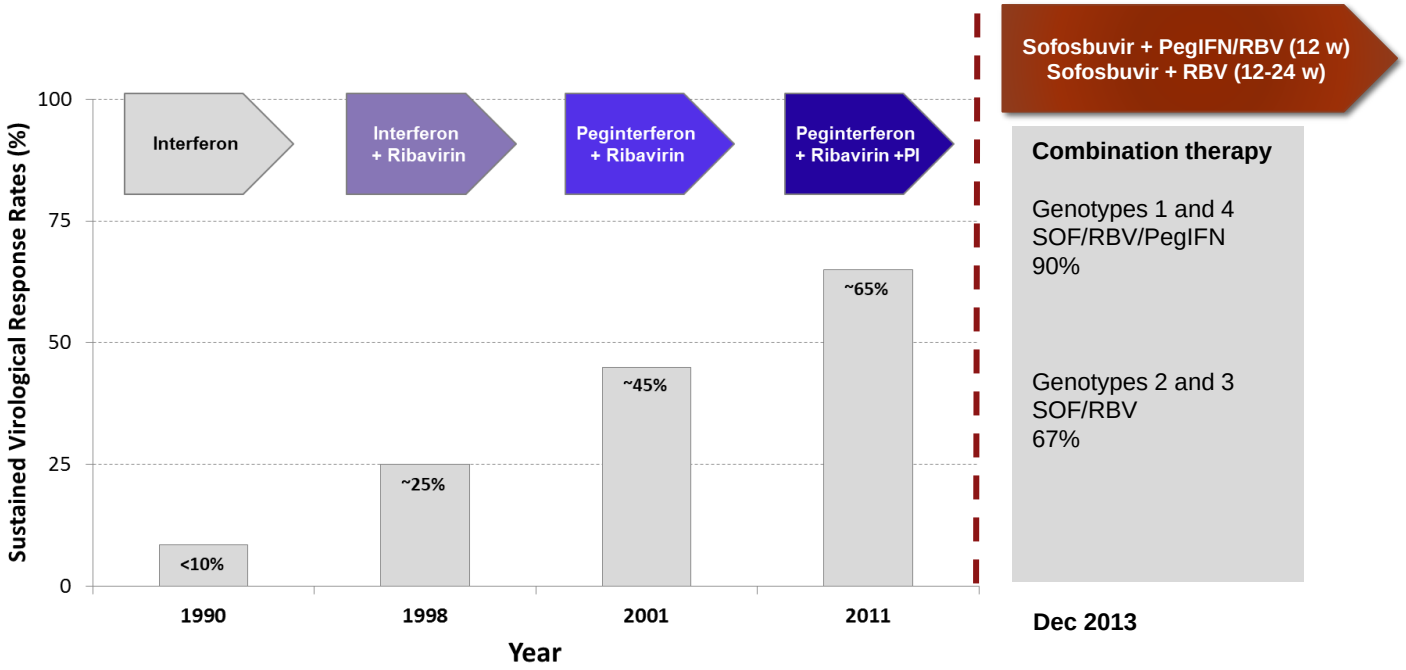
1. *Lancet*, VOLUME 385, ISSUE 9973, P1124-1135, MARCH 21, 2015

Dec 2013, Sovaldi® was approved as part of combination therapy for HCV

Changes in Standard of Care for HCV and Improvements in Numbers of SVR*



Sofosbuvir is a potent and selective inhibitor of non-structural protein 5B (NS5B)

- Effective against HCV genotypes 1, 2, 3 and 4
- Administered in combination with other drugs
- Route of Administration : 400 mg/day QD

SVR means that HCV virus is not detected in the blood ≥ 12 weeks after completing treatment

Ideal properties of an HCV single tablet regimen containing sofosbuvir

Target Product Profile (TPP)

Once daily dosing

Orally administered

Immediate release (IR) tablet formulation

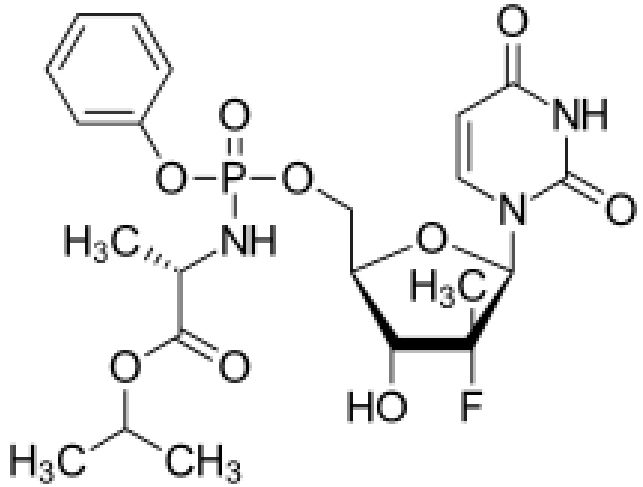
All agents contained within a single tablet

Minimal drug-drug interactions

No food effect

Robust intra-/inter-patient performance

Developing a single tablet regimen (STR) containing sofosbuvir



Sofosbuvir (SOF)

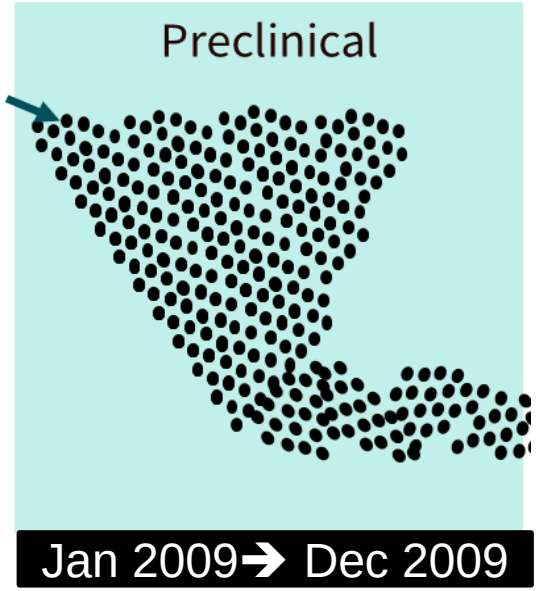
- uridine phosphoramidate pronucleotide
- NSA5B inhibitor

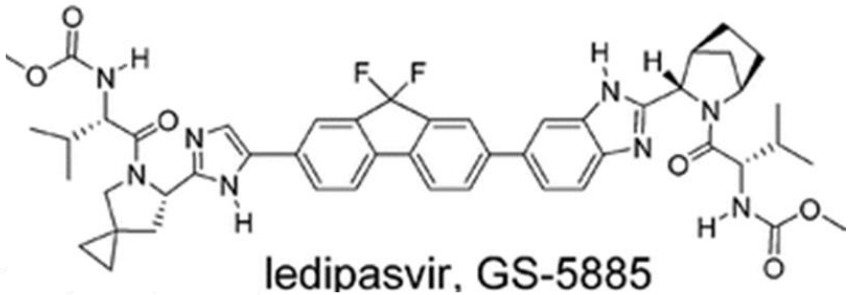
Required key attributes for the 2nd Agent[1]:

- NS5A inhibitors targeting mainly GT1
- Sufficient potency and metabolic stability to achieve a low dose
- Half-life compatible with once-daily dosing
- Suitable drug interaction profile for combination with other HCV antivirals of complementary mechanism

[1] J. O. Link, *HCV : The Journey from Discovery to Cure, Oct 2019*

Ledipasvir (LDV), an NS5A inhibitor, was highly potent against HCV with a long half life suitable for once daily dosing



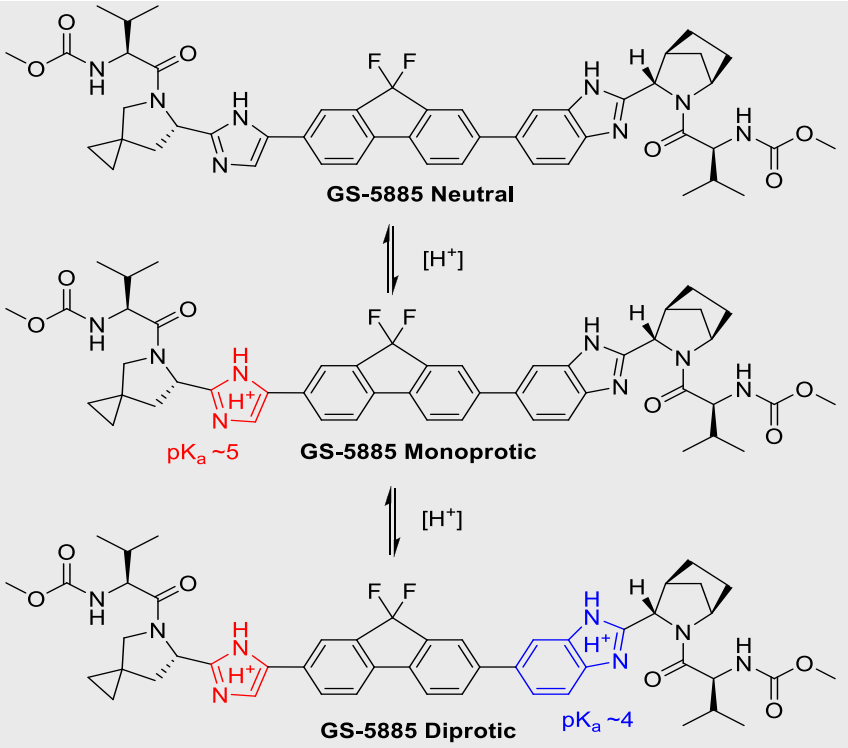


- ☑ **Potent** NS5A inhibitor targeting mainly GT1 (EC_{50} of 31 pM for GT1a)[1]
- ☑ **Low** predicted human metabolic hepatic **clearance**: 0.012 L/h/kg[1]
- ☑ BCS II (high permeability/low solubility) with a Log P 3.8

[1] J. O. Link, *Journal of Medicinal Chemistry*. 57 (5): 2033–2046

Potential biopharmaceutical limitations of a poorly soluble weak base, such as LDV

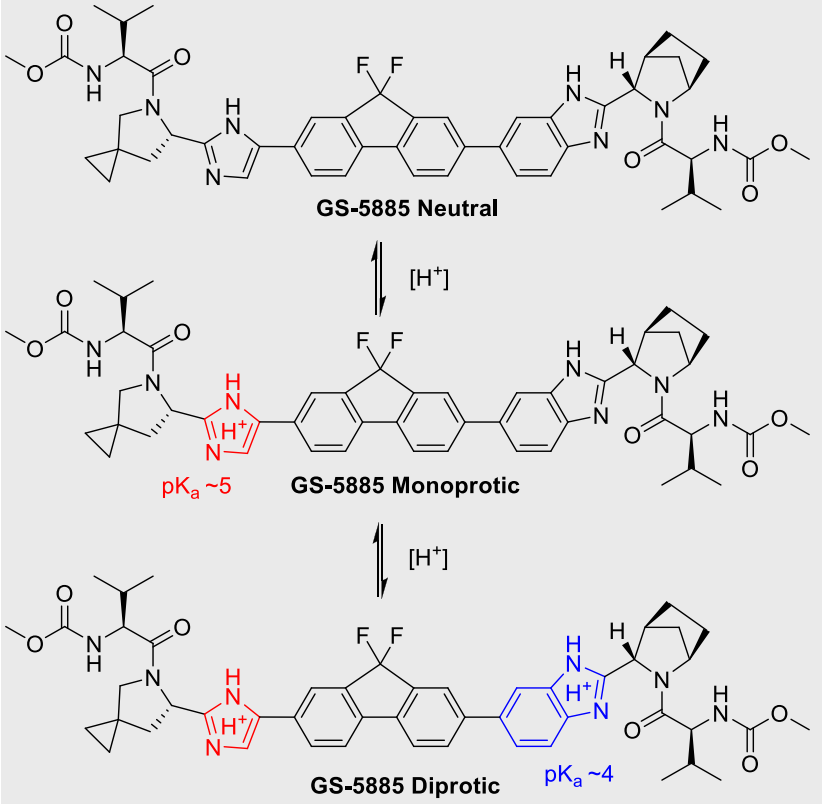
LDV has 2 pK_a : 4 (benzimidazole)
5 (imidazole)



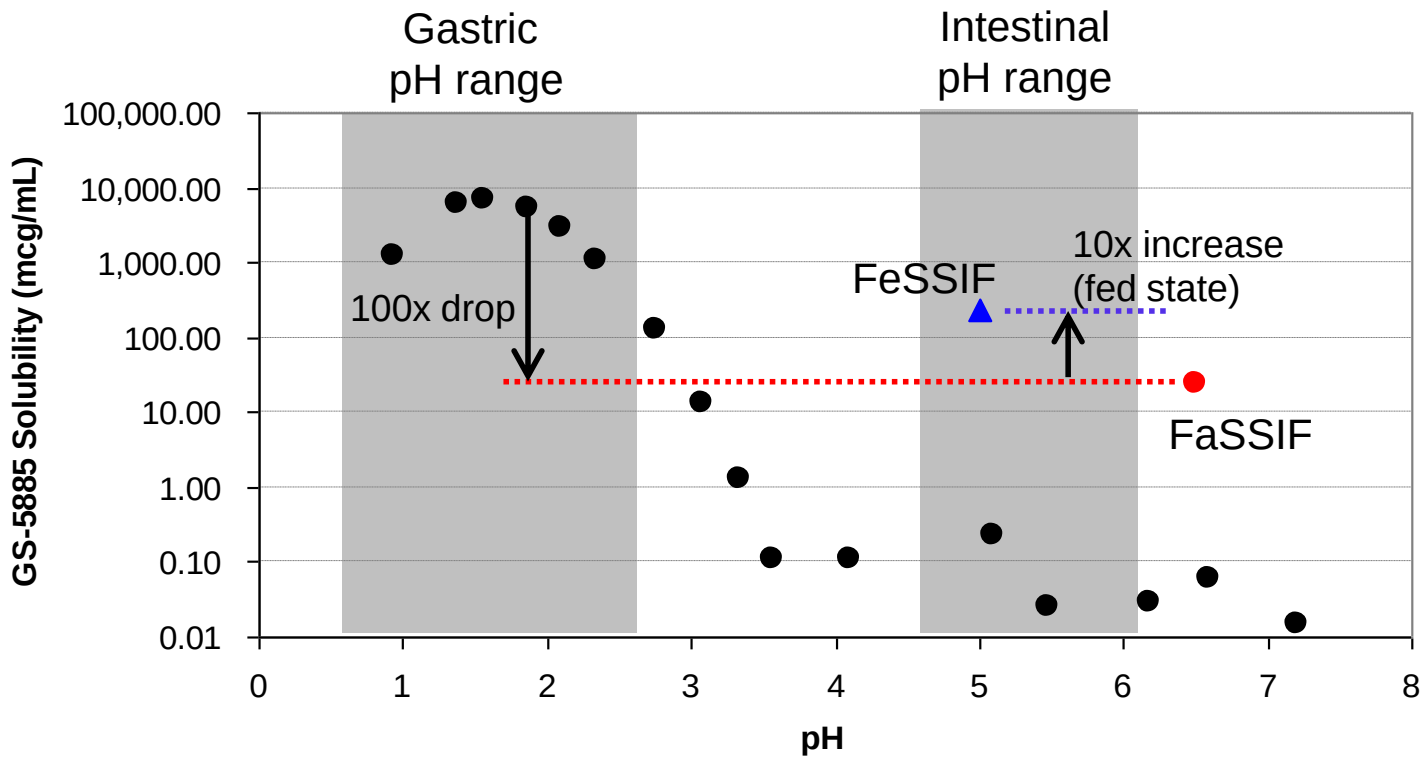
- Biopharmaceutical performance is **dissolution limited**
  - A drug is classified as 'poorly soluble' when its dissolution rate is considered so slow that dissolution takes longer than the transit time past the prime absorptive region in the gastrointestinal tract
- Low or non-linear bioavailability :
  - When administered in conventional solid dose formulations, these compounds have a tendency to exhibit low bioavailability as their absorption is described as dissolution rate limited.
- High intra- and inter-subject **variability**
- pH-dependent solubility : **DDI** with acid reducing agents (ARA)
- Significant **food effect**

C.M. O'Driscoll et al., Advanced Drug Delivery Reviews 60 (2008) 617–624
Horter, D et al., Advanced Drug Delivery Reviews 1997, 25, 3.

LDV is a “poorly soluble” weak base with a 100x difference in solubility between simulated gastric and intestinal media



In-vitro Model for Predicting ARA and Food Effects

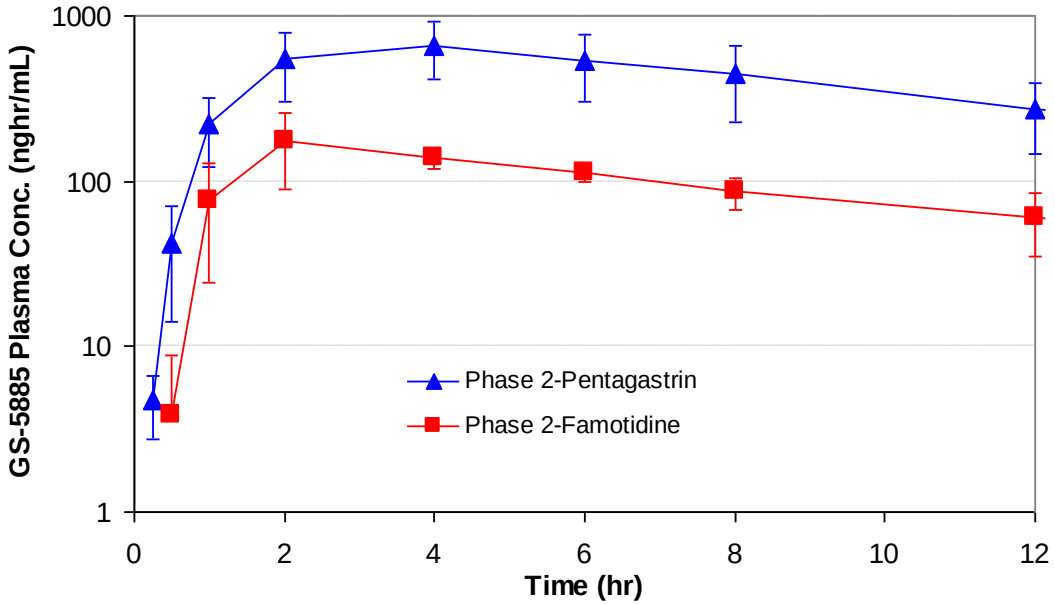


1 FaSSIF is water with 3mM sodium taurocholate and 0.75 mM lecithin, pH adjusted to 6.5 with phosphate buffer, ionic strength adjusted to 0.15M with NaCl.

2 FeSSIF is water with 15 mM sodium taurocholate and 3.75 mM lecithin, pH adjusted to 6.5 with phosphate buffer, ionic strength adjusted to 0.15M with NaCl.

Plasma exposure of LDV from an IR tablets was reduced 7-fold in dogs in the presence of an ARA (famotidine)

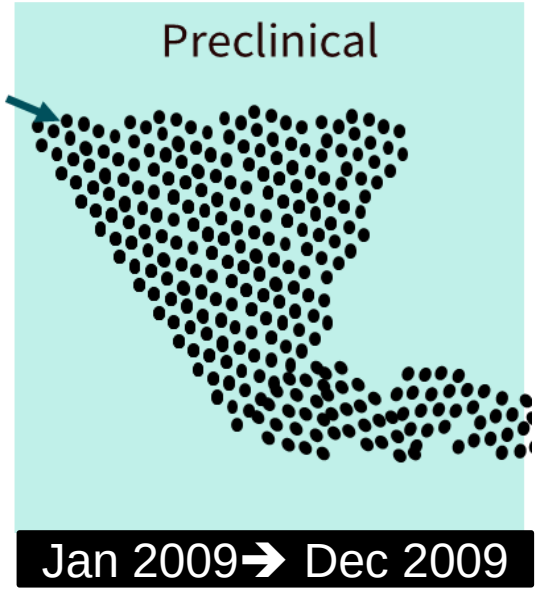
Effect of pH on Bioavailability in the Dog Model

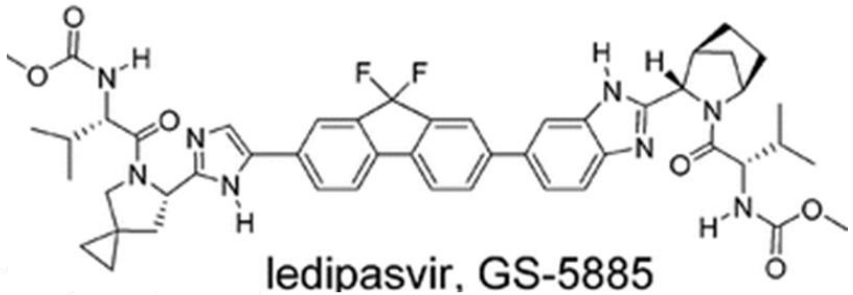


In-vivo Models for Predicting ARA Effects

Formulation	LDV (IR Tablet)	
Pretreatment	**Pentagastrin**	**Famotidine**
C_{max}	665 (254)	154 (68)
T_{max}	4.00 (0.00)	2.67 (1.03)
$AUC_{0\rightarrow24}$	7623 (3380)	1038 (427)
F%	67%	9%

Ledipasvir (LDV), an NS5A inhibitor, was highly potent against HCV with a long half life suitable for once daily dosing





- ☑ **Potent** NS5A inhibitors targeting mainly GT1 (EC_{50} of 31 pM for GT1a)[1]
- ☑ **Low** predicted human metabolic hepatic **clearance** : 0.012 L/h/kg[1]
- ☑ Sufficient potency and metabolic stability to achieve a **low dose**
- ☑ **Long half-life** compatible with once-daily dosing ($t_{1/2}$: 4.7 to 103 h in rat, dog, and monkey)[1]
- ☑ No significant adverse findings in 14-day rats and dogs tox studies [1]
- ☒ **Food effect and acid reducing agent DDI**

[1] J. O. Link, *Journal of Medicinal Chemistry*. 57 (5): 2033–2046

Approaches to overcome solubility/dissolution limited bioavailability of LDV

Key Selection Criteria :

- Biopharmaceutical performance
- Manufacturability
- In vitro dissolution profile
- Drug product stability

LDV Forms

- Amorphous
- Crystalline Tartaric Salt

Dosage Forms:

- Liquid Filled Capsules

- Solid Dosage Forms
  - Powder In Capsule

  - Immediate Release Tablet

Dry Granulation Process

Wet Granulation Process (Addition of Surfactants)

WO 2010/132601 International Publication Number WO 2014/120981

A “conventional” IR tablet using a crystalline salt of LDV was selected for clinical trials

PK Performance of LDV following an oral administration of LDV liquids and oral solids in pentagastrin pretreated beagle dogs[1]

LDV API Form	Dosage Type	Process	Dose (mg)	$AUC_{0\rightarrow24}$ (nM* hr)	C_{max} (nM)	F (%)
Amorphous Free Base	Non- Precipitating Solution [a]	N/A	25	—	—	53
	Powder in Capsule [b,e]	Blend	25	—	—	18
	IR Tablet[c,e]	HSWG DG	25	—	—	71
Crystalline D-Tartrate Salt	IR Tablet[d,e]	DG	25	7,623	665	68
			90	18,086	1,831	54

[a] Solution was composed of 5/45/50 EtOH/PEG 400/water (50 mM citrate buffer, pH 3), n=3

[b] Administered as neat amorphous GS-5885 free base in hard gelatin capsule, n=3

[c] Administered as amorphous GS-5885 free base formulated into a tablet containing LDV/filler: Disintegrant: Lubricant

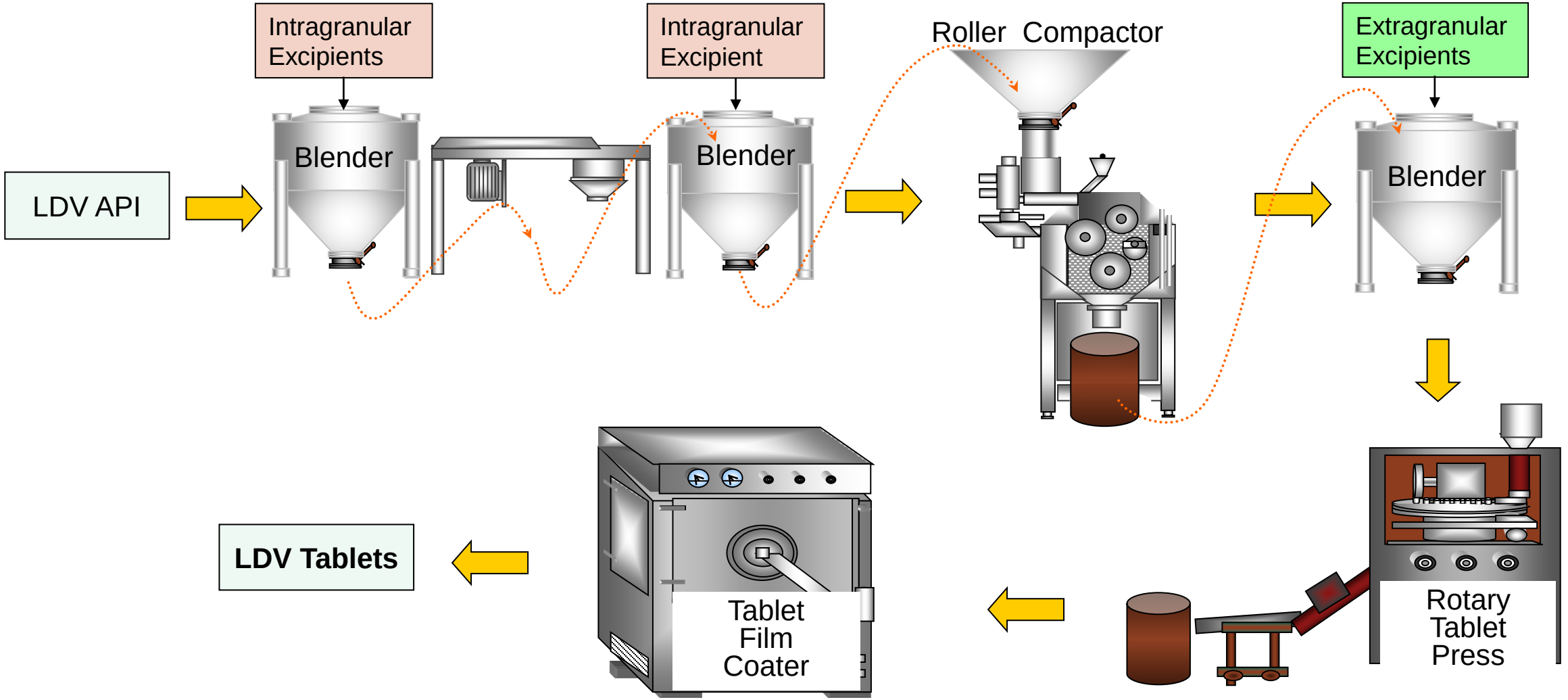
[d] Administered as crystalline GS-5885 D-tartrate salt formulated into a tablet containing LDV/filler: Disintegrant: Lubricant

[e] Pentagastrin pretreated

HS: High Shear Wet Granulation ; DG : Dry Granulation

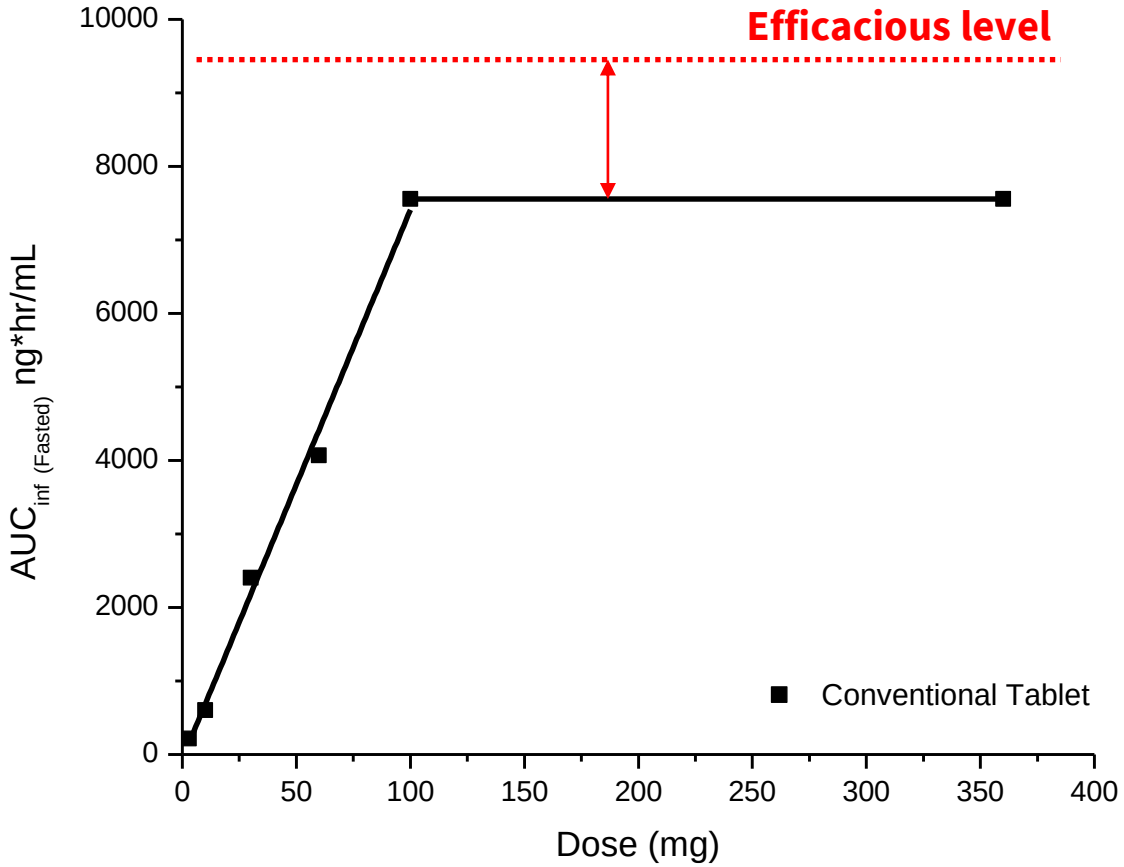
[1] Mogalian et al., US Patent Application Pub. No.: US 2014/0212487 A1, July 31 2014

The “conventional” LDV tablet was prepared using a dry granulation process



The “conventional” tablet containing the crystalline salt of LDV had limited exposure and a negative food effect in healthy volunteers

Non-Linear Dose Response



Negative Food Effect

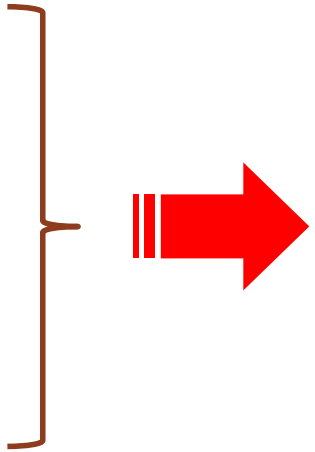
Administration (30 mg)	Conventional AUC inf (ng*hr/mL)
Fasted	2450
Fed	1225

~ 50% decrease

A non-conventional formulation was required to improve the biopharmaceutical performance

Approaches to improve biopharmaceutical performance of LDV

☑ Salt formation or
❑ Prodrug strategy
☑ Acid/base modifiers
☑ Particle size reduction
☑ Incorporation of wetting agents/surfactants



Conventional LDV formulation

- pH-dependent absorption
- Non-linear dose response
- Negative food effect

Further formulation development required to address limitation

❑ Solubilized formulations
☑ Amorphous solid dispersions

Amorphous Solid Dispersion

- Dissolution and solubility enhancement

Amorphous solid dispersions can improve drug exposure and bioavailability by increasing the solubility and dissolution rate of a drug

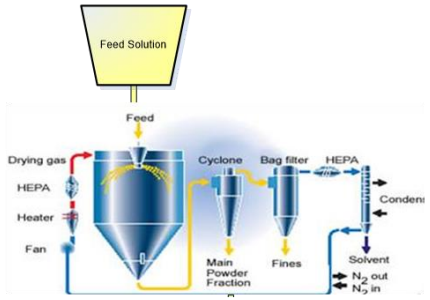
1. C. Leuner, *Eur. J. Pharm. Biopharm.*, 50 (2000), pp. 47-60

Amorphous solid dispersions can improve drug exposure and bioavailability by increasing the solubility and dissolution rate of a drug

Solid Dispersion

* Drug Substance
* Hydrophilic Matrix

Solvent → **Spray Drying**



High Shear/Temp → **Melt Extrusion**

Solid dispersion is a method which involves dispersion of one or more active ingredients in an inert carrier prepared by melting, dissolution in solvent, or solvent evaporation method[1]

- Molecular dispersion occurs in solution (drug and polymer dissolved in a solvent)
- Solution is then sprayed and dried into a solid

- Molecular dispersion occurs at a temperature higher than the melt temperature of the drug and/or excipient
- Mixture is then cooled and resulting solid is milled for further processing

1. S. Verma, et al. Int. J. Pharm. Tech., 3 (2011), pp. 1062-1099

Benefits and challenges of spray drying

Benefits:

- Create amorphous material
- Solubility enhancement
- Improves exposure and bioavailability by increasing the solubility and dissolution rate of a drug
- Engineer particles
- Continuous scalable process
- Material reprocessing

Challenges:

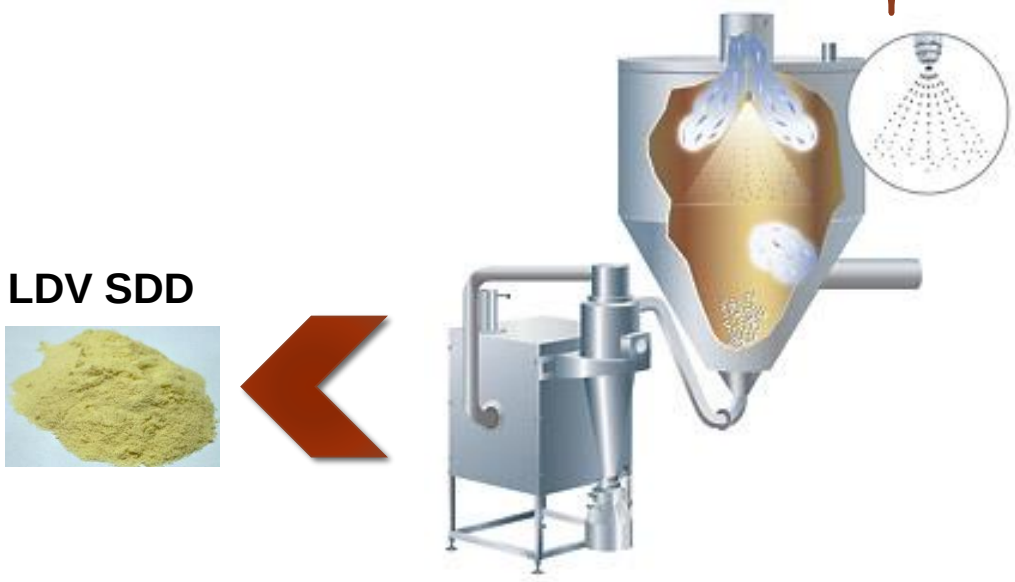
- Physical stability (nucleation)
- Hygroscopic

Development of a spray-dried dispersion (SDD) of LDV required selection of several variables

LDV Forms
- Amorphous
- Crystalline Tartaric Salt
- **LDV Acetone Solvate**

Carrier : Non-ionic polymers
- Hypromellose (HPMC)
  T_g 150 ºC
- **Copovidone** (Kollidon VA 64)
  T_g 110 ºC

Solvent (LDV solubility > 500 mg/mL)
- **EtOH**
- DCM
- MeOH



LDV SDD

Evaluated the **solubility**, stability, in-vitro and in-vivo performance

1 : 1
LDV Acetone Solvate : Copovidone

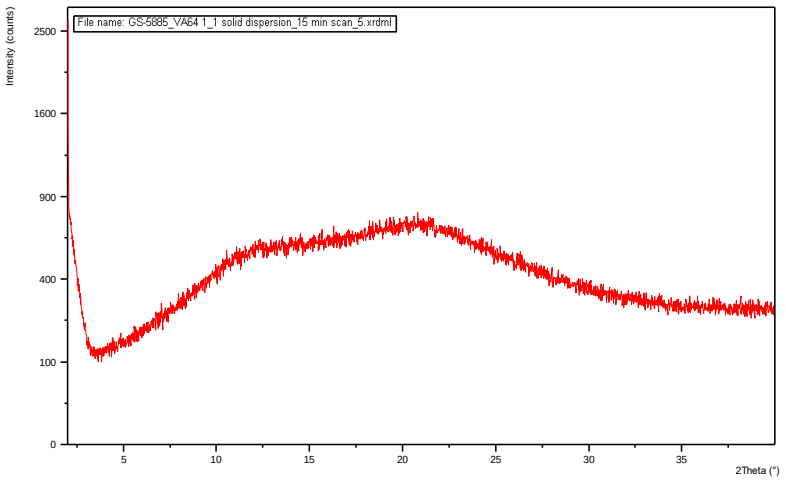
[1] Mogalian et al., US Patent Application Pub. No.: US 2014/0212487 A1, July 31 2014

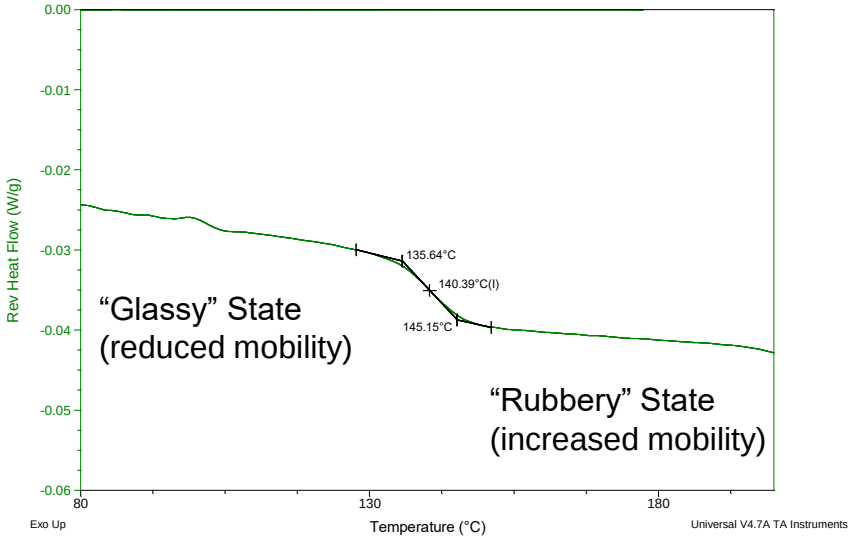
LDV SDD is amorphous and hygroscopic

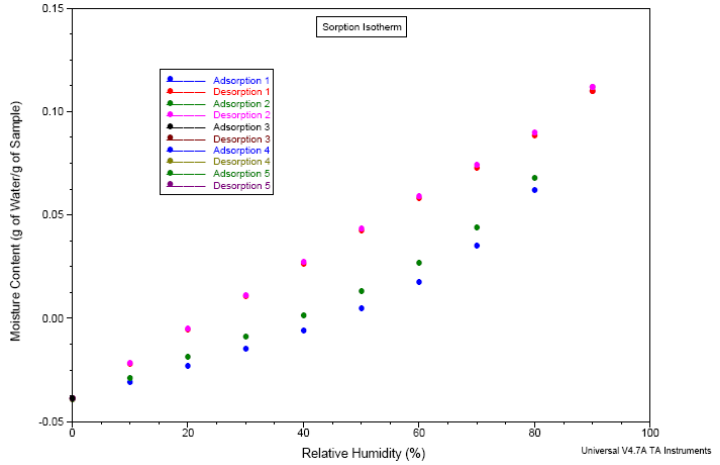
Amorphous by Powder X-ray Diffraction
- Improved solubility/dissolution rate

High Glass Transition Temperature
- Lower likelihood to crystallize

Hygroscopic (Adsorbs Water Vapor)
- Increased risk of crystallization if exposed to elevated humidity

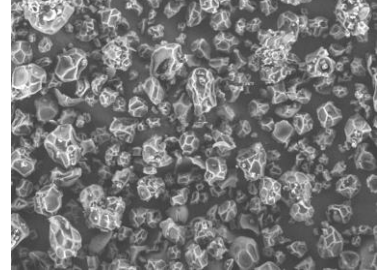


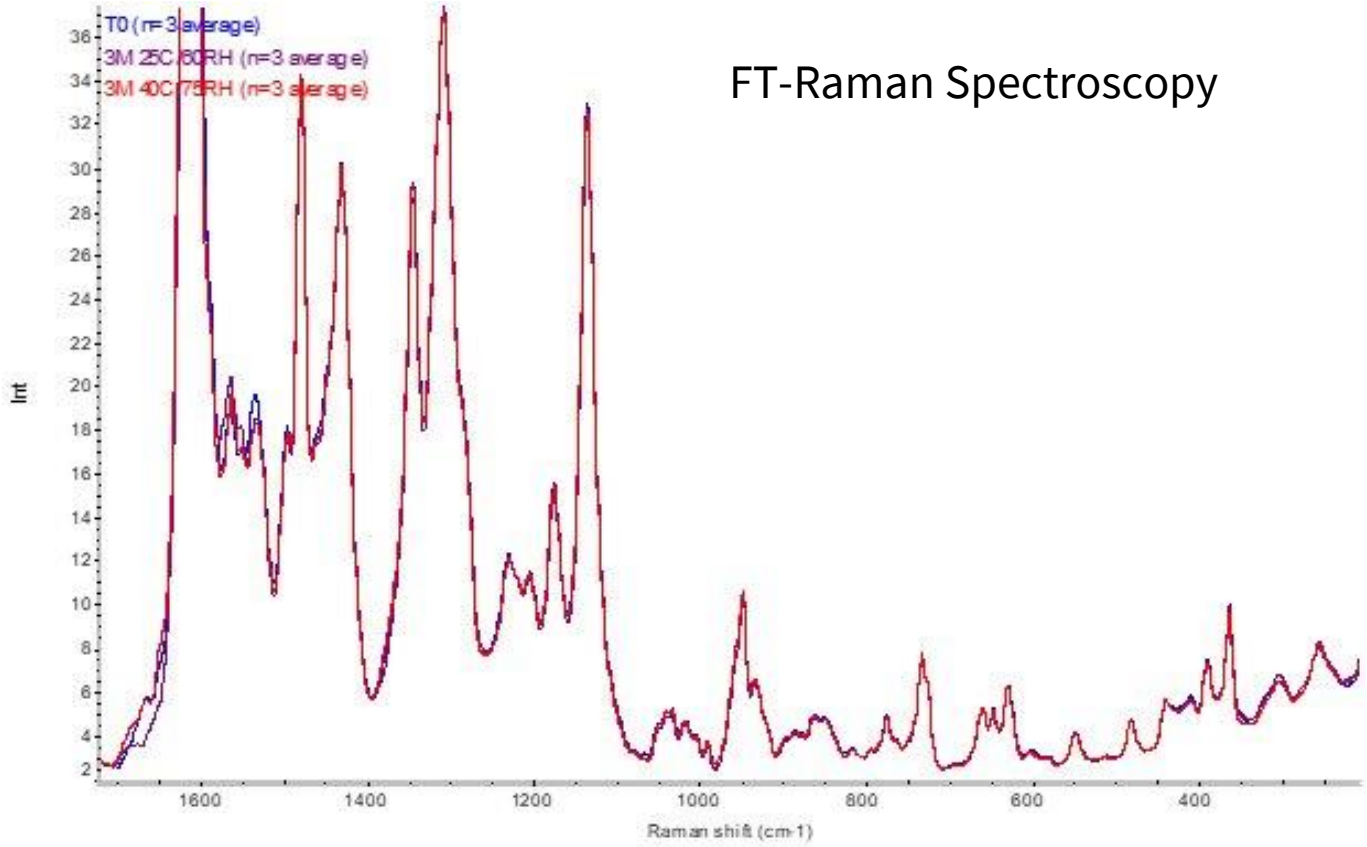




[1] Mogalian et al., US Patent Application Publication Number : US 2014/0212487
[2] Chal et al. , International Publication Number WO 2014/120981

LDV SDD is physically stable under open and closed conditions





FT-Raman Spectroscopy

Time Point (months)	25 °C/60% RH Closed	40 °C/75% RH Closed
0	Amorphous	Amorphous
3	Amorphous	Amorphous

LDV SDD stored under open conditions at 40 °C/75% RH for up to 6 months demonstrates no tendency for crystallization or phase transition.

[1] Mogalian et al., US Patent Application Publication Number : US 2014/0212487
[2] Chal et al. , International Publication Number WO 2014/120981

LDV SDD is Chemically stable for up to 6 months under accelerated condition

Stability Condition		Current Time point (months)	LDV Label Strength (%)	TotalDeg./Imp.(% AN)
N/A		Initial	49.6	0.2
50°C/92% RH	Open	1- week	50.3	0.2
40°C/75% RH	Open	1- month	50.1	0.2
	Closed	3-Month	49.9	0.2
25°C/60% RH	Closed		49.4	0.2

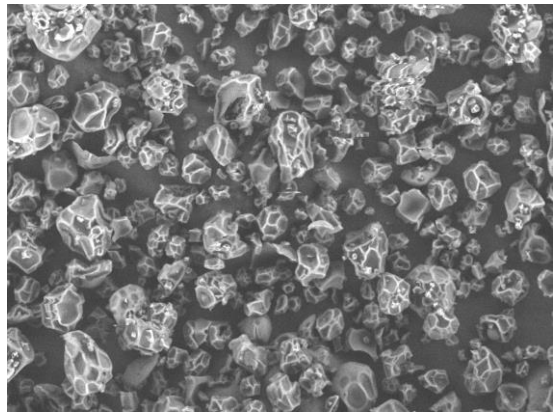
[1] Mogalian et al., US Patent Application Publication Number : US 2014/0212487
[2] Chal et al. , International Publication Number WO 2014/120981

LDV SDD is Chemically stable for up to 6 months under accelerated conditions

Stability Condition		Time point (months)	LDV Label Strength (%)	Total Degradant / Impurity Content (% AN)
N/A		Initial	49.6	0.2
50°C/92% RH	Open	1 week	50.3	0.2
40°C/75% RH	Open	1 month	50.1	0.2
	Closed	3 Month	49.9	0.2
25°C/60% RH	Closed		49.4	0.2

[1] Mogalian et al., US Patent Application Publication Number : US 2014/0212487
[2] Chal et al., International Publication Number WO 2014/120981

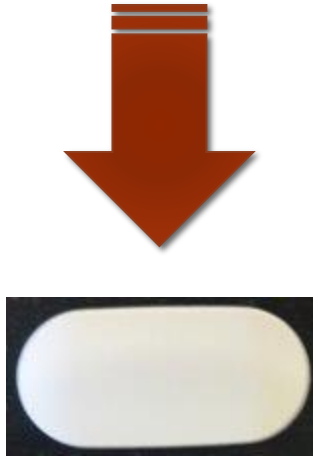
LDV SDD has suitable properties for tablet development



- ☑ Amorphous
- ☑ Has a high T_g 140 °C implying that LDV SDD has a low propensity to crystallize
- ☑ Hygroscopic and requires proper handling and packaging condition
- ☑ Physically Stable under open condition by FT-Raman and X-ray diffraction
- ☑ Chemically stable for up to 6 months under accelerated condition

Is the LDV SDD tablet going to:

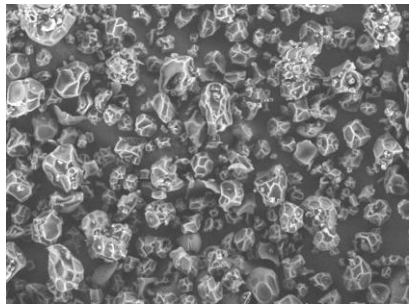
- Enhanced exposure
- Eliminate DDI with ARA?
- Reduce Food effect?
- Patient to Patient Variability?



[1] Mogalian et al., US Patent Application Publication Number : US 2014/0212487
[2] Chal et al. , International Publication Number WO 2014/120981

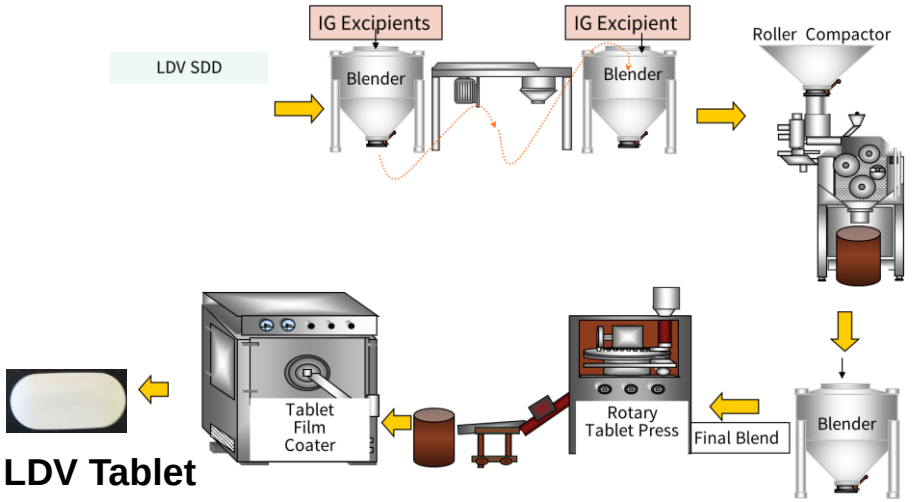
New LDV tablet formulation was developed using LDV SDD to overcome the DDI and food effects

LDV SDD



LDV Tablet

LDV Tablet Formulation	Composition (% w/w)
LDV SDD	30.00
Fillers	64.00
Disintegrant	5.00
Lubricant	1.0
Total Core Weight (mg)	600



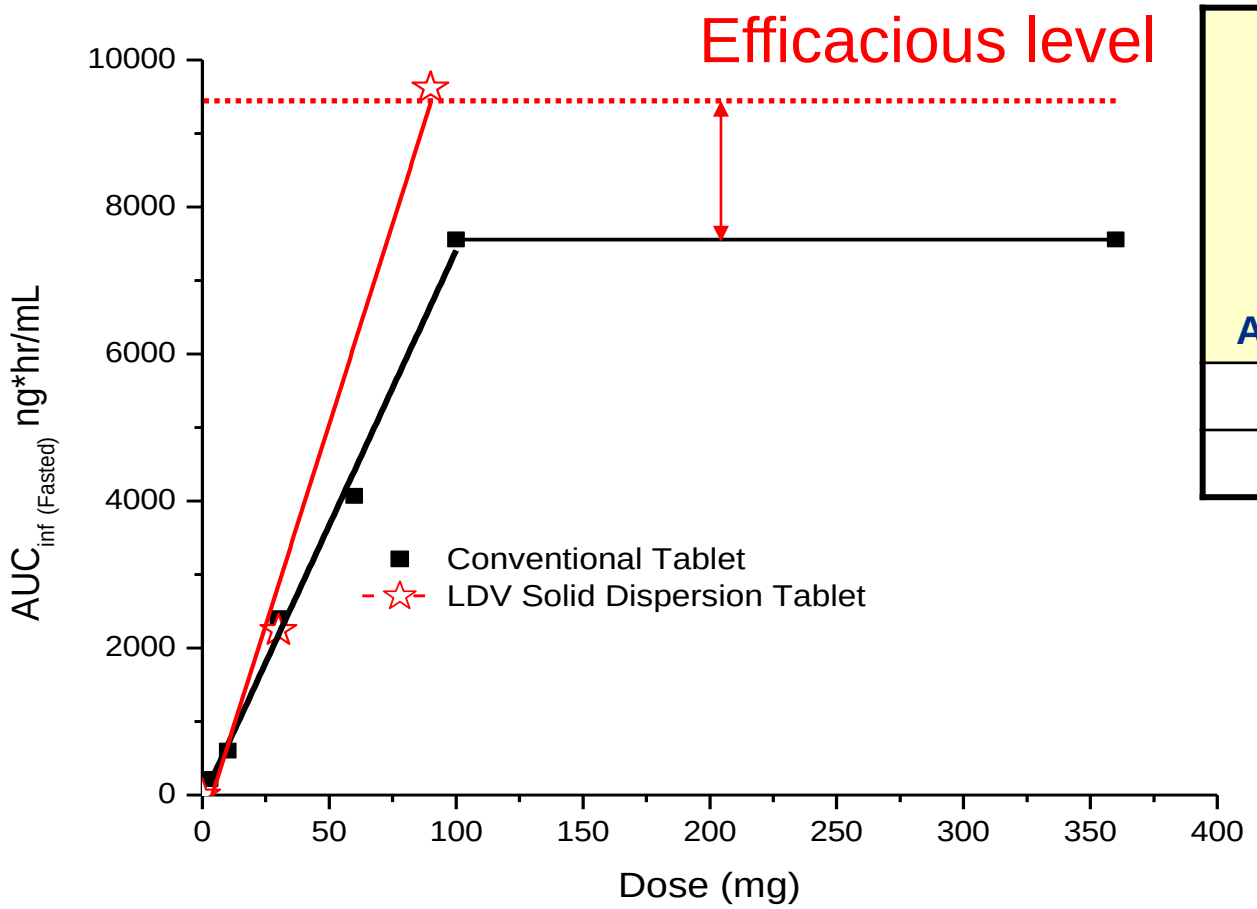
Plasma exposure from LDV SDD tablets has similar exposure to non-precipitating solution in famotidine pretreated dogs

Pharmacokinetic Parameters of LDV after Oral Administration of LDV Tablets to Fasted Beagle Dogs[1]

Formulation	Non-Precipitating Solution	Conventional Tablet		LDV SDD Tablet (1:1)	
Dose (mg)	30	30	30	30	30
Pretreatment	Famotidine	Pentagastrin	Famotidine	Pentagastrin	Famotidine
C_{max}	369 (96)	665 (254)	154 (68)	983 (22)	393 (119)
$AUC_{0\rightarrow24}$	3383 (1266)	7623 (3380)	1038 (427)	10541 (24)	3930 (20)
F%	**30%**	**67%**	**9%**	**93%**	**35%**

[1] Mogalian et al., US Patent Application Pub. No.: US 2014/0212487 A1, July 31 2014

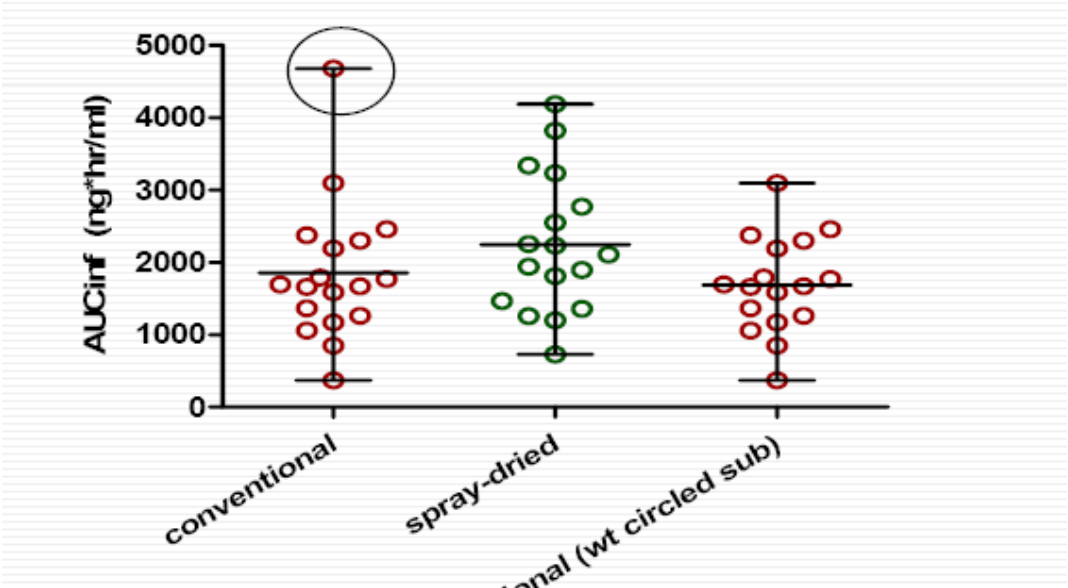
Tablet containing LDV SDD improved the biopharmaceutical performance and eliminated the negative food effect



Administration	Conventional Tablet 30 mg Dose AUC inf (ng*hr/mL)	SDD Tablet 90 mg Dose AUC inf (ng*hr/mL)
Fasted	2450	9610
Fed	1225	10100

[1] Mogalian et al., US Patent Application Pub. No.: US 2014/0212487 A1, July 31 2014

Patient-to-patient variability was reduced using the LDV SDD



Summary Stats AUC_{inf} (ng*hr/mL)	Conventional Tablet	GS-5885 ASD Tablet	Conventional Tablet (w/o circled patient)
N	18	17	17
Median	1680	2105	1670
Range	367, 4678	726, 4183	367, 3094
Max/Min	12.7	5.8	8.4

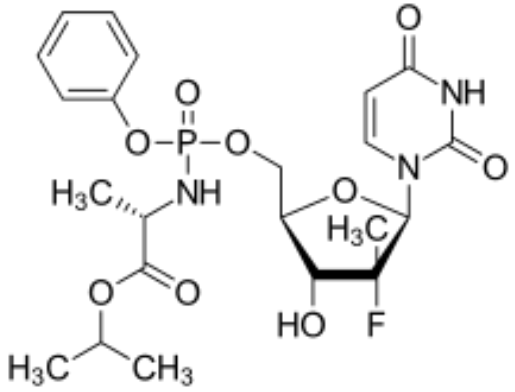
Tablets containing LDV SDD did not overcome the DDI with ARA's

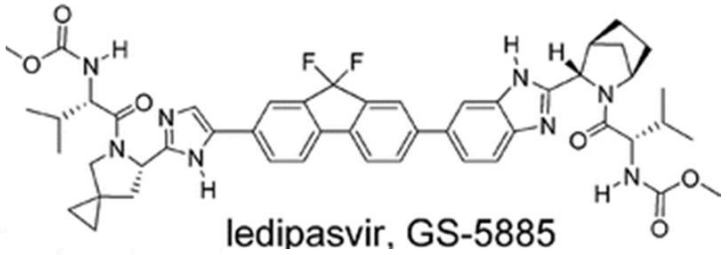
Ledipasvir, Solid Dispersion (N = 17)			
Mean (%CV)	**Ledipasvir alone**	**Ledipasvir + Omeprazole**	**%GMR (90%CI)**
AUC_{inf} (ng.hr/mL)	2140 (38.8)	1300 (50.7)	58.5 (48.3, 70.8)
AUC_{last} (ng.hr/mL)	1850 (33.5)	1070 (45.5)	56.3 (46.4, 68.3)
C_{max} (ng/mL)	64.8 (32.9)	36.2 (55.9)	52.2 (41.4, 65.9)

Clinical trials of LDV SDD tablet formulation showed improvement over the “conventional” tablet formulation

- ✓ Improved the dissolution rate limited biopharmaceutical performance
- ✓ Increased bioavailability / improved linearity
- ✓ Reduced the patient-to-patient variability
- ✓ Eliminated the negative food effect
- ☒ Did not significantly improve clinical exposure in the presence of ARA’s

Developing a single tablet regimen containing 400 mg SOF and 90 mg LDV





- Single tablet
- Total weight of < 1200 mg
  - 400 mg SOF
  - 90 mg LDV (180 mg SDD)
- Comparable pharmacokinetic performance to single agents
- Physically and chemically stable
- Manufacturing process:
  - ➢ Commercially scalable
  - ➢ Commercially robust
- Room temperature storage

Sofosbuvir (SOF)

- NS5B
- Dose 400 mg
- BCS III
  (high solubility, low permeability)
- Crystalline Form II (T_m 123 ºC)
- Non hygroscopic
- Physically and chemically stable
- Sovaldi tablet: 1200 mg tablet

Ledipasvir (LDV)

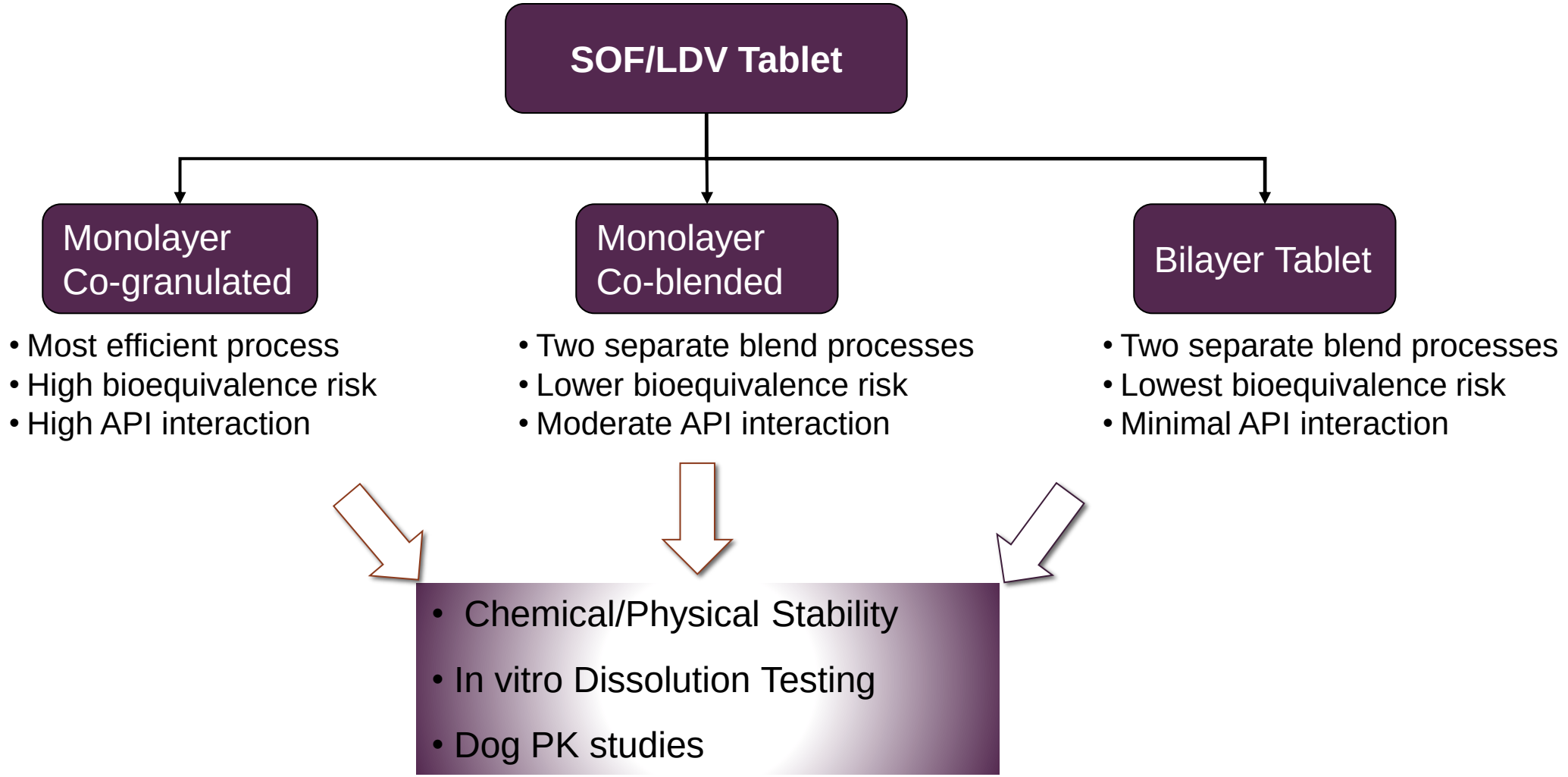
- NS5A
- Dose 90 mg (180 mg of SDD)
- BCS II
  (Low Solubility, High Permeability)

LDV SDD

- Amorphous
- Hygroscopic
- Physically and chemically stable
- LDV SDD tablet: 600 mg tablet

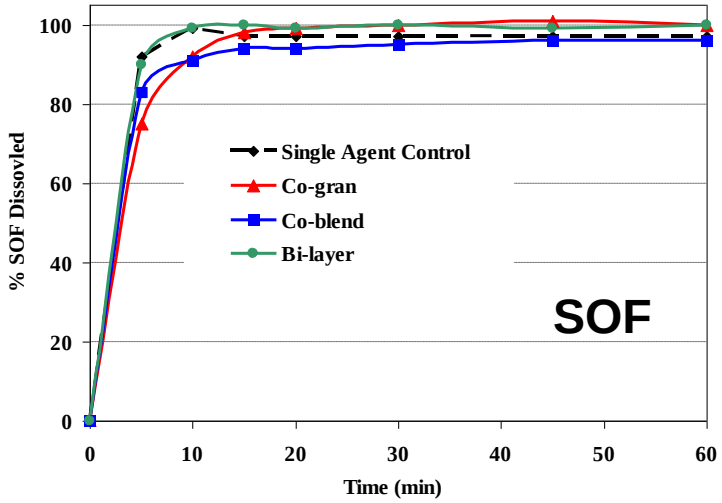
[1] *Chal et al., International Publication Number WO 2014/120981*

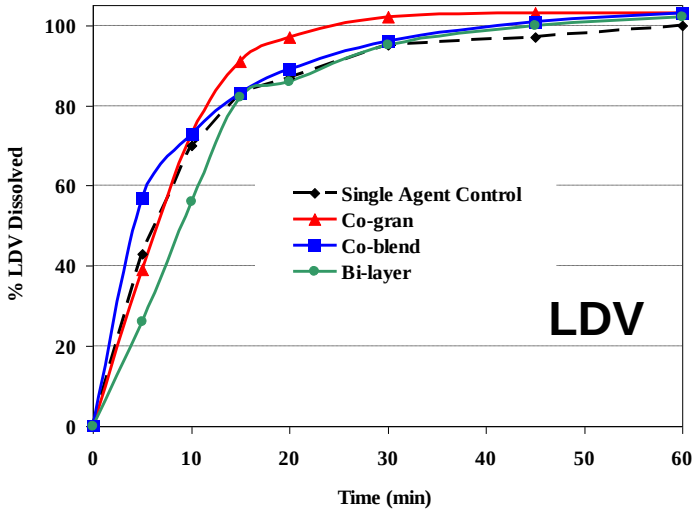
Various manufacturing processes were evaluated to develop an STR for SOF/LDV containing 400 mg of SOF and 90 mg of LDV



[1] *Chal et al., International Publication Number WO 2014/120981*

All SOF/LDV tablet formulation prototypes have comparable dissolution and dog PK performance





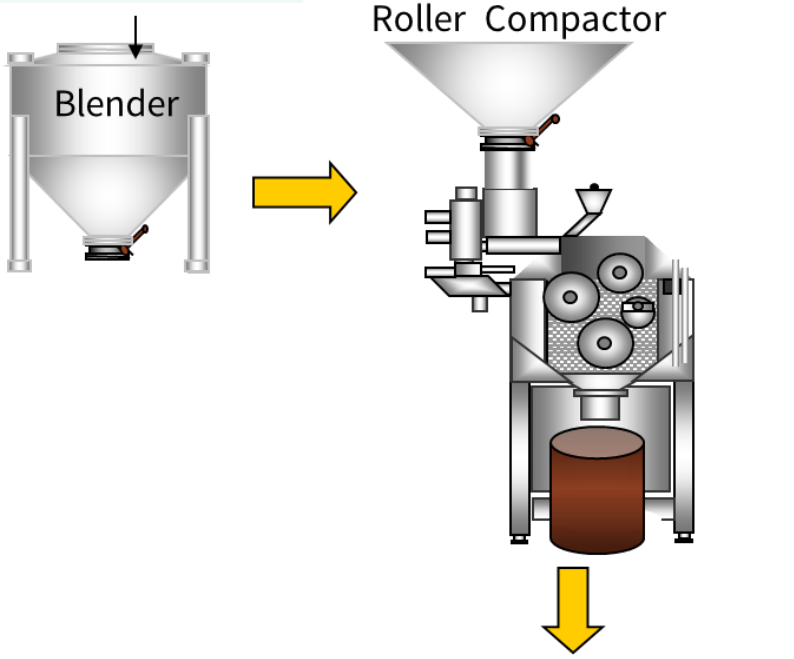
Total Tablet weight /Formulation	Treatment	SOF AUC_{0-t} (ng*hr/mL)	SOF C_{max} (ng/mL)	LDV AUC_{0-last} (ng*hr/mL)	LDV C_{max} (ng/mL)
Control SOF tablet + LDV SD tablet	Famotidine	314 ± 207	503 ± 363	3260 ± 1312	345 ± 132
Monolayer, Co-granulated	Famotidine	501 ± 249	729 ± 434	3236 ± 730	333 ± 56
Monolayer, Co-blended	Famotidine	483 ± 406	652 ± 527	4208 ±2216	444 ± 215
Bilayer	Famotidine	283 ± 193	288 ± 201	4,712 ± 2,270	421.7 ± 203.7

Plasma Concentration of SOF/LDV After Oral Administration of SOF/LDV FDC and Control Tablets in Fasted Dogs (100 mg/22.5 mg Fixed/Dog)

Dissolution Media: 10 Mm Phosphate Buffer pH 6.0, 1.5% Tween 80

LDV SDD and SOF API were chemically and physically compatible

LDV SDD: SOF
(1:2.2)



LDV SDD /SOF Co Blend

Stability

Monitor Stability for 4 weeks
60 ºC and 40 ºC/75% RH under open condition

✓ LDV SDD and SOF Compacts are Chemically Stable

Table 13: Strength and Impurity Content of Sofosbuvir and Ledipasvir: Copovidone Solid Dispersion Blend Stored at 40 °C/75% RH and 60 °C

		Ledipasvir		Sofosbuvir	
Condition	Time (weeks)	Strength (%)	Total Impurity Content (%)	Strength (%)	Total Impurity Content (%)
45 °C/75 % RH	0	98.8	0.0	102.9	0.4
	2	96.9	0.0	101.6	0.3
	4	97.1	0.0	100.5	0.2
60 °C	0	98.8	0.0	102.9	0.4
	1	99.2	0.0	102.4	0.3
	2	99.6	0.0	103.2	0.3
	4	98.9	0.0	102.8	0.2

✓ LDV SDD and SOF Compacts are Physically Stable

[1] *Chal et al., International Publication Number WO 2014/120981*

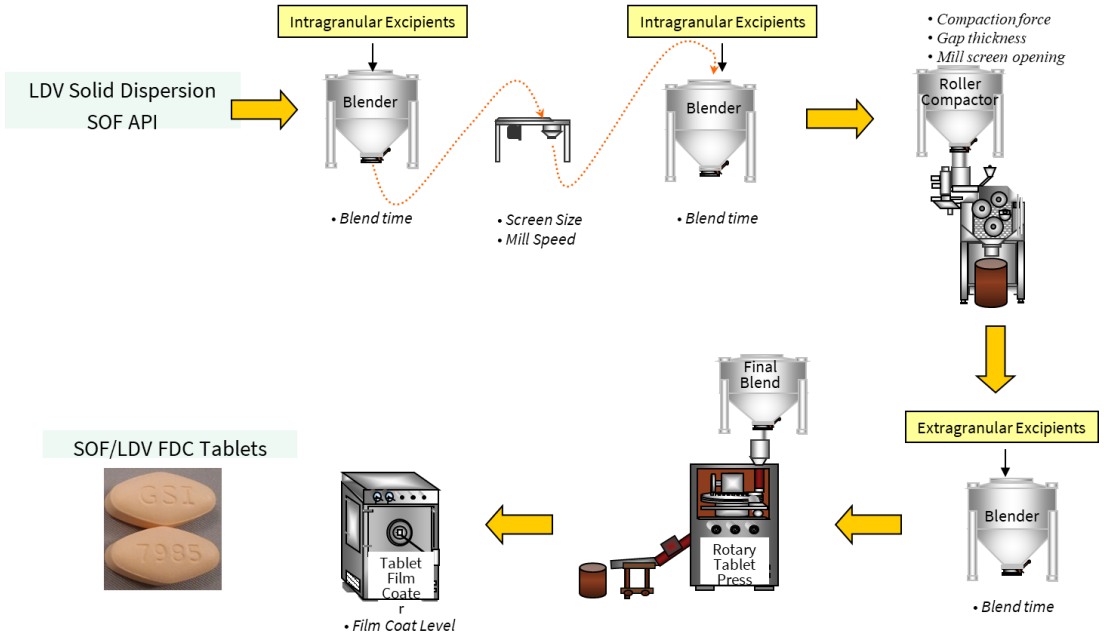
Monolayer
Co-granulated

A 1000 mg monolayer SOF/LDV tablet was the selected STR for clinical studies

Table 18. Composition of SOF 400 mg/Ledipasvir 90 mg FDC Tablets

Composition	% w/w
Intra-granular	
SOF	40.00%
Ledipasvir SD	18.00%
Lactose Fast Flow 316	16.50%
MCC 101	8.00%
Croscarmellose	2.50%
Silicon Dioxide	1.00%
Magnesium Stearate	0.75%
Extragranular	
MCC 101	10.00%
Croscarmellose	2.50%
Magnesium stearate	0.75%
Total Fill weight Core Tablet (mg)	**1000**
Coating	
Opadry II Orange 85F13912	3.0%
Water	QS

[1] *Chal et al., International Publication Number WO 2014/120981*



- Physically stable after 24 weeks in the absence of desiccant (FT-Raman)
- Tablets exposed to high moisture were physically and chemically stable
- Tablets were chemically stable in the proposed packaging configuration
- Shelf-life of 2 y below 30 ºC

SOF/LDV tablet and corresponding single agent tablets were bioequivalent when dosed in healthy volunteers[1]

LDV Tablet

SOF Tablet

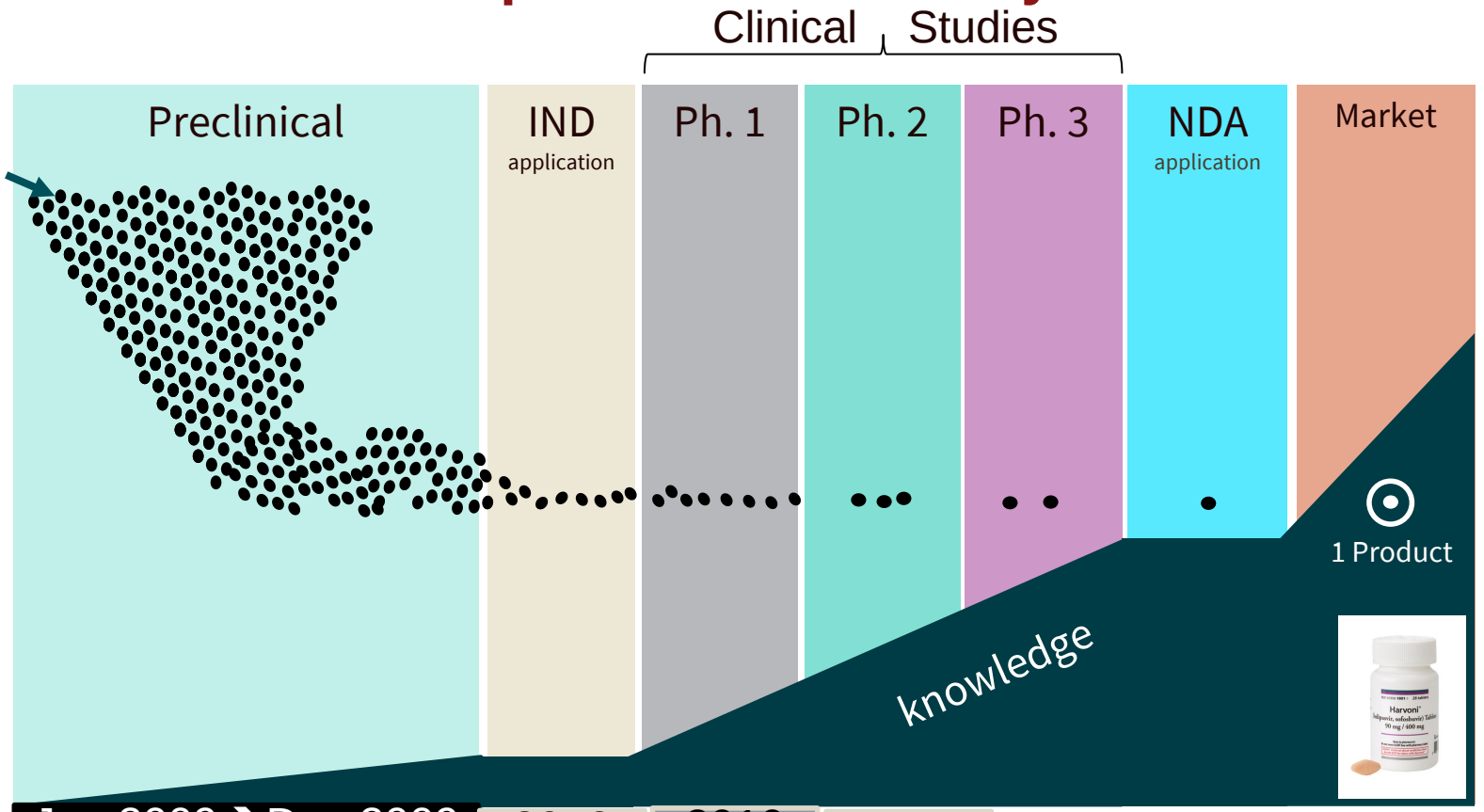
SOF/LDV Tablet

Total Tablet weight /Formulation	Dose (mg)	Sofosbuvir (SOF)		Ledipasvir (LDV)	
		AUC_{inf} (ng*hr/mL)	C_{max} (ng/mL)	AUC_{inf} (ng*hr/mL)	C_{max} (ng/mL)
Signle Agent Control SOF tablet + Ledipasvir SD tablet	SOF 400 mg Ledipasvir 90 mg	11900 (23.5)	764 (27.3)	9620 (45.6)	314 (40.5)
SOF/Ledipasvir FDC Tablet		12500 (23.1)	784 (36.2)	9570 (46.6)	314 (45.2)

24 healthy volunteers under fasted conditions

[1] *Chal et al., International Publication Number WO 2014/120981*

SOF/LDV tablet was developed in less than 2 years

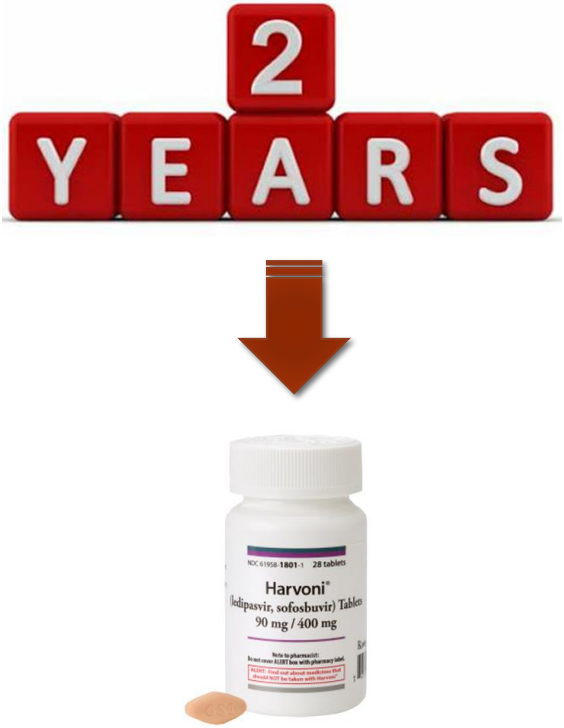


LDV Jan 2009➔Dec 2009 | 2010 | 2010 | 2012 | 2013 | 2014

SOF 2012 | 2012 | 2013 | 2014 | 2014

SOF/LDV US approval Oct 10, 2014; EU approval Nov 17, 2014

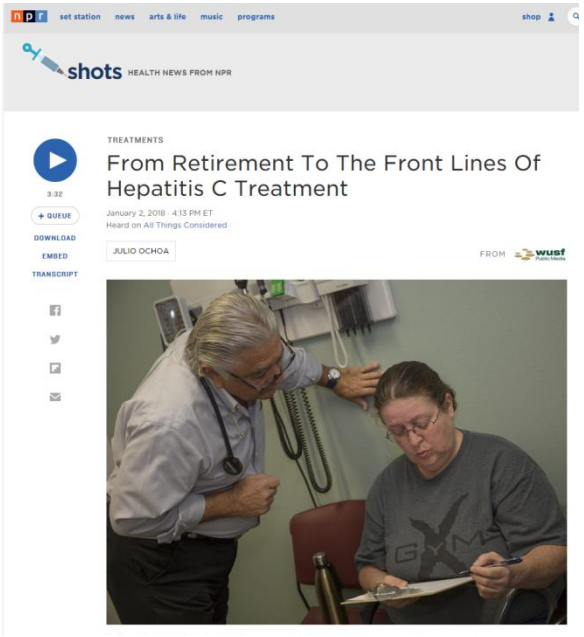
Harvoni® (LDV/SOF) tablets were developed in less than 2 years!



- ✓ Single tablet regimen containing 90 mg of LDV and 400 mg SOF
- ✓ Tablet weight is 1000 mg
- ✓ Developed a 1000 mg co-granulated monolayer tablet formulation using an amorphous SDD of LDV in combination with SOF
  - Developed and scaled-up a spray drying process
  - Developed and scaled-up a tablet process up to 450 kg
  - Developed a physically and chemically stable tablet containing amorphous SDD
  - All GMP batches of SOF 400 mg/LDV 90 mg film-coated tablets met acceptance/release criteria
- ✓ Demonstrated bioequivalence for the SOF/LDV tablet to the LDV and SOF single agent tablets
- ✓ Administered once daily
  - with or without food
  - with famotidine or omeprazole

Approval of Harvoni® (LDV/SOF) in 2014 improved HCV treatment options

Gilead Sciences improved HCV treatment when it rolled out Harvoni. Harvoni delivered mid-90% cure rates in as little as 8 to 12 weeks with limited adverse reactions



“Cirillo specialized in treating hepatitis C for more than 30 years before retiring. During his time, the only available treatment for hepatitis C had terrible side effects and it didn't work very well. It cured the viral infection less than half the time. But the newer drugs Harvoni and Solvaldi cure almost everybody, with few adverse reactions.”

"In my lifetime I've seen it change from a horrible treatment to a manageable treatment"

Harvoni®, Gilead's 1st once-daily STR for chronic 3 years of age and older with Genotype 1, 4, 5, or 6

Harvoni is used to treat chronic hepatitis C in adults and children who are at least 3 years old. Harvoni is sometimes given in combination with another medicine called ribavirin

Table 1 Recommended Treatment Regimen and Duration for HARVONI in Patients 3 Years of Age and Older with Genotype 1, 4, 5, or 6 HCV

HCV Genotype	Patient Population	Treatment Regimen and Duration
Genotype 1	Treatment-naïve without cirrhosis or with compensated cirrhosis (Child-Pugh A)	HARVONI 12 weeks*
	Treatment-experienced† without cirrhosis	HARVONI 12 weeks
	Treatment-experienced† with compensated cirrhosis (Child-Pugh A)	HARVONI 24 weeks‡
	Treatment-naïve and treatment-experienced† with decompensated cirrhosis (Child-Pugh B or C)	HARVONI + ribavirin§ 12 weeks
Genotype 1 or 4	Treatment-naïve and treatment-experienced† liver transplant recipients without cirrhosis, or with compensated cirrhosis (Child-Pugh A)	HARVONI + ribavirin§ 12 weeks
Genotype 4, 5, or 6	Treatment-naïve and treatment-experienced†, without cirrhosis or with compensated cirrhosis (Child-Pugh A)	HARVONI 12 weeks

* HARVONI for 8 weeks can be considered in treatment-naïve genotype 1 patients without cirrhosis who have pretreatment HCV RNA less than 6 million IU/mL [see Clinical Studies (14.2)].

† Treatment-experienced adult and pediatric subjects have failed a peginterferon alfa +/- ribavirin based regimen with or without an HCV protease inhibitor.

‡ HARVONI + ribavirin for 12 weeks can be considered in treatment-experienced genotype 1 patients with cirrhosis who are eligible for ribavirin [see Dosage and Administration (2.3 and 2.4) and Clinical Studies (14.2)].

§ See Dosage and Administration 2.3 and 2.4 for ribavirin dosage recommendations.

https://www.drugs.com/dosage/harvoni.html

Thank you
for your attention