Enhancing Oral Bioavailability of Felodipine Using Solid Self-Micro Emulsifying Drug Delivery Systems

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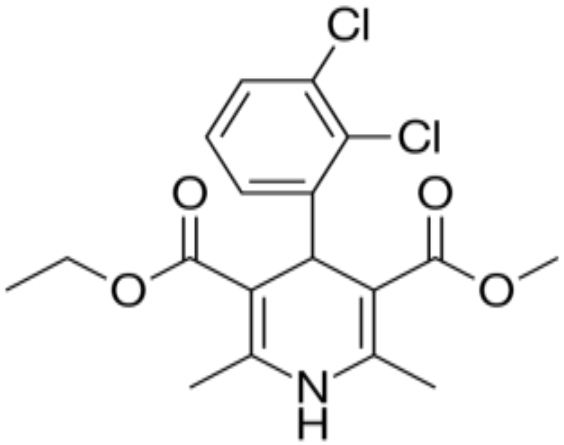
***Abstract*—Developing a drug product with improved solubility and bioavailability is a challenge for poorly water-soluble drugs such as Felodipine. The aim of the present work was to develop a solid self-micro emulsifying drug delivery system (SMEDDS) of Felodipine to improve its solubility and dissolution rate. Solubility of Felodipine was determined in various oils, surfactants, and co-surfactants, and the micro emulsion region was identified by constructing a pseudo ternary phase diagram using the water titration method. Stable SMEDDS was prepared using a combination of Tween 20 and PEG 600 (2:1) with clove oil (7.5% v/v), and liquid SMEDDS was subsequently converted into solid SMEDDS (S-SMEDDS) by adsorption onto Aerosil 200 as a solid carrier. The S-SMEDDS was evaluated for micromeritic properties and in-vitro drug release, with results showing a cumulative drug release of 99% within 90 minutes, a particle size of 78.3 nm, a zeta potential of -17.4 mV, and a polydispersibility index of 0.27. These findings conclude that S-SMEDDS is a promising solid dosage form that significantly improves the solubility, dissolution rate, and oral bioavailability of Felodipine.**

***Index Terms*—S-SMEDDS, Pseudo ternary phase diagram, bioavailability, dissolution rate.**

I. INTRODUCTION

Various techniques are used to enhance oral bioavailability of poorly water-soluble drugs. Oral route has been the major route of drug delivery for the chronic treatment of many diseases as it offers a high degree of patient compliance. Nearly 40% of new drug candidates exhibit low solubility in water, which is a challenge in development of optimum oral solid dosage form in terms of formulation design and bioavailability of new pharmaceutical products. Many strategies have been used to overcome these problems either by means of modifying the solubility or maintaining the drug in dissolved form throughout gastric transit time. Self-emulsification systems are one formulation technique that can be a fitting answer to such problems.

The major advantages of this technology are its general applicability to most drug and its simplicity. This is the case of class II drug, e.g., Felodipine (according to the BCS classification). Self-micro emulisifying drug delivery system (SMEDDS) is defined as isotropic mixtures of natural or synthetic oils, solids or liquid surfactant, that have a unique ability of forming fine oil-in-water (o/w) MEs upon mild agitation followed by dilution in aqueous media, such as GI fluids. SMEDDS formulation having transparent and bluish appearance, with particle size in range of 1 to 100 nm. Felodipine is an anti-hypertensive drug which acts as a calcium channel blockes to inhibit the influx of calcium ions to decreases the arterial smooth muscle contraction.



II. MATERIALS AND METHODS:

Materials

Table :1 Materials

MATERIALS	MANUFACTURER
Felodipine	Sri Krishna pharmaceutics
Clove oil	Research lab fine chemicals
Tween 20, Tween 40	Oxford lab chemicals
Tween 60	Sisco Research Laborateries
Propylene glycol	Research lab fine chemicals
PEG 600	Oxford lab chemicals
Aerosil 200	Himedia laboratories

Methods:

Solubility study:

OIL:

2ml of each component was taken in screw cap vials with known quantity (250mg) of drug. A vortex mixer was used to facilitate the solubilization. Sealed vials were kept on isothermal mechanical shaker at 40±2°C for 72 hours. After equilibrium, each test tube was centrifuged at 6000rpm for 20min. Supernatant was filtered through membrane filter using 0.45µm filter disk. Filtered solution was appropriately diluted with methanol and concentration of felodipine was determined using UV spectrophotometer at 364 nm.

SURFACTANT AND CO-SURFACTANT:

Surfactant selection was done on the basis of % transparency

Take 500µL surfactant and 500µL of oil phase in a beaker. Heated at 50°C for the homogenization of the components. Each mixture, 100µL, was then diluted with 50ml distilled water in glass stopper conical flask. The % transparency was evaluated by UV spectrophotometer using distilled water as blank.

Pseudo ternary phase diagram

The existence of microemulsions regions were determined by using pseudo-ternary phase diagrams. SMEDDS were diluted under agitation conditions using water titration method. Oil, surfactants and co surfactants were grouped in four different combinations for phase studies. Surfactant and co surfactants (Smix) in each group were mixed in different weight ratios (1:1, 2:1, 3:1, 4:1). Nine different combinations of oil and Smix were made so that maximum ratios were covered for the study to delineate the boundaries of phases precisely formed in the phase diagrams. The concentration of water at which turbidity-to-transparency and transparency-to-turbidity transitions occurred was derived from the weight measurements. These values were then used to determine the boundaries of the microemulsion domain corresponding to the chosen value of oils, as well as the S/CoS mixing ratio.

Preparation of liquid SMEDDS:

Felodipine was incorporated in oil phase, warmed on water bath at 40°C. Surfactant and co-surfactant measured separately and mixed with previously prepared oil phase. The resulting mixture is vortexed on magnetic stirrer till drug is completely solubilized. The resulting solution was kept at room temperature until used.

Preparation of solid SMEDDS:

Aerosil 200 (180 mg) used as a solid carrier, for conversion of liquid SMEDDS to solid. The conversion process involved addition of liquid formulation (2 ml) onto carriers under continuous mixing in a blender, sieved after mixing. The powder was dried and filled directly into capsules.

CHARACTERIZATION OF SMEDDS

1. Thermodynamic stability:

a) Heating cooling cycle:

Six cycles between refrigerator temperature 4˚C and 45˚C with storage at each temperature of not less than 48h was studied. Those formulations, which were stable at these temperatures, were subjected to centrifugation test.

b) Centrifugation:

Passed formulations were centrifuged at 3500 rpm for 30min. Those formulations that did not show any phase separation were taken for the freeze thaw stress test.

c) Freeze thaw cycle:

Three freeze thaw cycles between 4˚C and +25 ˚C with storage at each temperature for not less than 48h was done for the formulations. Those formulations, which passed these thermodynamic stress tests, were further taken for the dispersibility test for assessing the

efficiency of self-emulsification. The formulations were observed visually for any phase separation or color change

2. Dispersibility test:
The efficiency of self-emulsification of oral SMEDDS was assessed using a USP dissolution apparatus 2. One milliliter of each formulation was added to 500 ml of water at 37±0.5 ˚C. A standard stainless steel dissolution paddle rotating at 50 rpm provided gentle agitation. The *in-vitro* performance of the formulations was visually assessed using the following grading system:
Grade A: Rapidly forming (within 1 min) microemulsion, having a clear or bluish appearance.
Grade B: Rapidly forming, slightly less clear microemulsion, having a bluish white appearance.
Grade C: Fine milky microemulsion that formed within 2 m.

3. Particle size distribution (PSD):
SMEDDS formulation was diluted 100 times with distilled water and 6.8 pH buffer, at 37 ± 0.5˚C. The resultant emulsions were prepared by gentle agitation for 10 min using a magnetic stirrer.

4. % Transmittance Measurement:
The percent transmittance of various formulations was measured at 254 nm using UV spectrophotometer keeping water as a blank formula include.
%T=antilog (2-absorbance)

5. Micro meritic properties of S-SMEDDS:
Prepared S-SMEDDS was evaluated for micro meretic properties such as angle of repose, bulk and tapped density, compressibility index and Hausner ratio.

6. Polydispersibility Index (PDI):
Polydispersibility which determines size range of particles in the system is measured by;

$$\frac{\text{No. of particles having size greater than 100 nm}}{\text{No. of particles having size less than 100 nm}}$$

It is expressed in terms of polydispersibility index (PDI). An ideal SMEDDS should be widely distributed with particles less than 100 nm and so PDI should be less than 0.3.

7. In *vitro* Release studies:
Dissolution Test: The dissolution test was conducted using intestinal fluid (phosphate buffer, pH-6.8) as dissolution medium. Using intestinal fluid, 900 ml of 6.8 pH buffers was placed in the vessel and allowed to come to 37 ± 0.5° C. Then, felodipine S-SMEDDS were placed in six baskets, one in each basket and stirrer was rotated at 100 rpm for above 1 hr.

III. RESULT

Table 2: Solubility of Felodipine in Excipients:

Ingredients	Solubility (mg/ml)
Oils	
Caster oil	8.50±4.24
Olive oil	3.87±2.40
Isopropylmyristate	2.78±1.44
Clove oil	110±1.25
Surfactants	
Tween 20	120±2.52
Tween 60	110±1.27
Tween 40	100±1.87
Co-surfactants	
PEG 600	120±3.44
Propyleneglyed	50±2.47

The solubility of Felodipine was detrmined in various oils, surfactants and co-surfactants. Among oils, Clove oil showed 110 mg/ml highest solubility. From all surfactants Tween 20(120 mg/ml) showed highest solubility. For co-surfactants, PEG 600, solubility was found to be 120 mg/ml. Based on solubility study Clove oil, Tween 20, 40, 60 and PEG 600 are selected as oil, surfactant and co-surfactant.

FTIR Compatibility studies:
FTIR spectra of pure Felodipine clove oil, Tween 20 combination are should in following figures

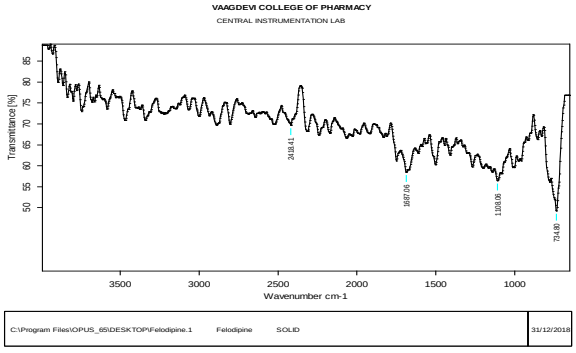


FIG 1: FTIR spectra of Felodipine

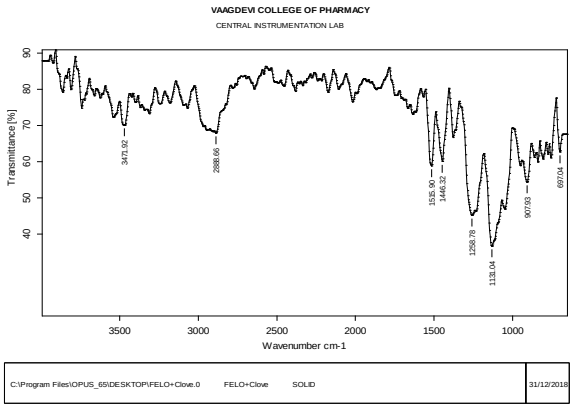


FIG 2: FTIR of Felodipine + clove oil

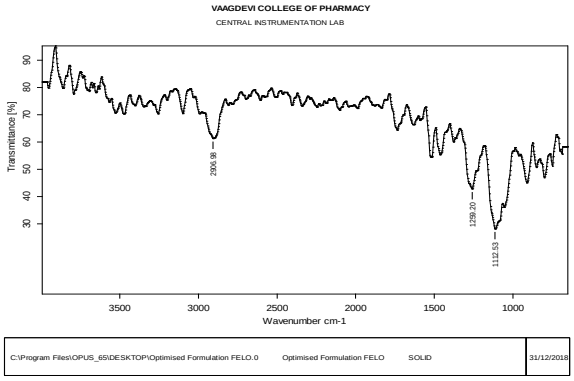


FIG 3: FTIR of Felodipine + clove oil + Tween 20

Table 3 FTIR studies of Felodipine+oil and surfactant

Infrared spectra	Peak of functional groups wavelength(cm^{-1})			
	C-Cl	C=C	C-O	-COOH
Felodipine	734	1637	1108	2418
Felodipine+clove oil	697	1515	1131	2888
Felodipine+clove oil+tween 20	712	1259	1112	2906

There was no appearance of dispersion of any characteristic peak in the FTIR spectrum of drug and polymers used. This shows that there is no chemical interaction between the drug and the surfactants used. The presence of peaks at the expected range confirms that the material taken for the study are genuine and there is no possible interaction.

Pseudo ternary phase diagram:

C1: Oil (clove oil), surfactant: co-surfactant (Tween 20: PEG 600) and water.

Table 4: Water titration Readings for phase diagram (C1)

Oil(ml)	Smix(ml)	Dilution with water until system remain clear(ml)			
		4:1(S:CoS)	3:1(S:CoS)	2:1(S:CoS)	1:1(S:CoS)
1	9	Infinite	Infinite	Infinite	Infinite
2	8	16	20.6	18.6	5.7
3	7	3.4	1.7	2.5	3.4
4	6	2.3	3.1	2	3.4
5	5	1.3	3.2	2.1	2.2
6	4	1.9	1	2.1	1.6
7	3	2.1	2.3	2.2	2.7
8	2	4.3	3	3.7	2
9	1	2.9	3.9	3.7	1.5

C1C (2:1)

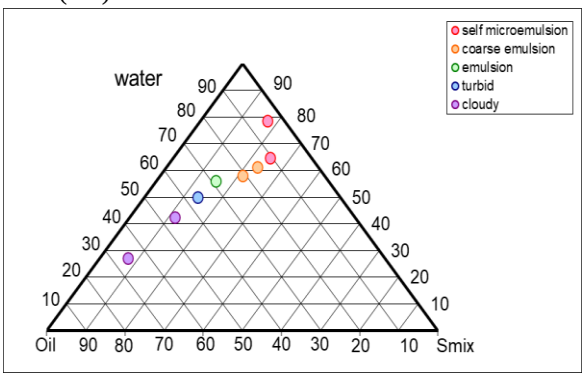


FIG 4: Ternary phase diagram of Tween20: PEG 600(2:1)

C2: Oil (clove oil), surfactant: co-surfactant (Tween60: Propyleneglycol) and water.

Table 5: Water titration Readings for phase diagram (C2)

Oil(ml)	Smix(ml)	Dilution with water until system remain clear(ml)			
		4:1(S:CoS)	3:1(S:CoS)	2:1(S:CoS)	1:1(S:CoS)
1	9	Infinite	Infinite	Infinite	Infinite
2	8	9.9	Infinite	Infinite	9.5
3	7	3	7.5	5.6	3.5
4	6	1.9	3	3.4	3.5
5	5	1.6	2.7	2.2	3.9
6	4	2	1.8	2.8	2.6
7	3	3.2	2.5	1.8	2.8
8	2	4	2.5	2	2.2
9	1	3.8	2.5	2.2	4

C2B (3:1)

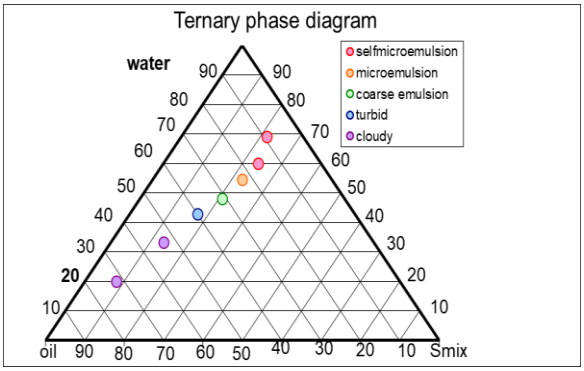


FIG 5: Ternary phase diagram of Tween60: propyleneglycol (3:1)

C3: Oil (clove oil), surfactant: co-surfactant (Tween 40: PEG 600) and water.

C3B (3:1)

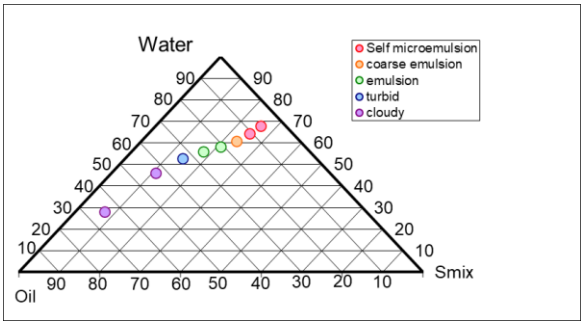


FIG 6: Ternary phase diagram of Tween 40: PEG 600(3:1)

From the below diagrams Tween 20: PEG 600(2:1), Tween 60: Propylene glycol (3:1) and Tween 40: PEG 600(3:1) were optimized for preparation of SMEDDS.

Table6: Water titration Readings for phase diagram (C3)

Oil(ml)	Smix(ml)	Dilution with water until system remain clear(ml)			
		4:1(S:CoS)	3:1(S:CoS)	2:1(S:CoS)	1:1(S:CoS)
1	9	Infinite	Infinite	Infinite	Infinite
2	8	Infinite	4	3.8	20
3	7	2	2.5	2.9	3
4	6	2	1.5	2.3	3
5	5	2	1.2	1.7	3
6	4	2	1.6	2.4	2.8
7	3	4.4	2.7	2.3	2.4
8	2	4	4.6	3.6	2.3
9	1	3.6	3.9	3.2	3.5

Table 7: Formulation of liquid SMEDDS of Felodipine with optimized ratios:(X-5%, Y-7.5%, Z-10% oil)

Formulation code	Felodipine (mg/ml)	Clove oil(%v/v)	Tween 20(2:1)	Tween 60(3:1)	Tween 40(3:1)	PEG 600	Propylene glycol
C1X	10	5	63.3	-	-	31.7	-
C1Y	10	7.5	61.7	-	-	30.8	-
C1Z	10	10	60	-	-	30	-
C2X	10	5	-	71.2	-	-	23.8
C2Y	10	7.5	-	69.4	-	-	23.1
C2Z	10	10	-	67.5	-	-	22.5
C3X	10	5	-	-	71.2	23.8	-
C3Y	10	7.5	-	-	69.4	23.1	-
C3Z	10	10	-	-	67.5	22.5	-

Evaluation of SMEDDS: Table 8

1. Thermodynamic stability and dispersibility test of different formulations

2.% Transmittance: The clarity ofmicroemulsions was checked by transparency, measured in terms of transmittance (%T). %T=antilog (2-absorbance)

Table 9:

Formulation code	Heating cooling cycle	Centrifugation	Freeze-thaw cycle	Dispersibility test	Inference
C1X	x	x	X	Xx	Failed
C1Y	√	√	√	+	Passed

C1Z	√	√	√	+	Passed
C2X	√	√	√	+	Passed
C2Y	√	√	√	+	Passed
C2Z	x	x	X	Xx	Failed
C3X	√	√	√	+	Passed
C3Y	x	x	X	Xx	Failed
C3Z	√	√	√	+	Passed

Formulation code	%Transmittance
C1Y	99.7
C1Z	99.3
C2X	98.8
C2Y	98.4
C3X	99.1
C3Z	98.2

3. Powder characteristics of all adsorbent after adsorption of liquid SMEDDS:

Table 10

Formulation code	Parameters					Inference
	Angle of response	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's Index %	Hausner's ratio	
C1Y	24	0.594	0.744	14.6	1.25	Excellent
C1Z	27	0.492	0.609	15	1.23	Good
C1X	30	0.397	0.543	16	1.36	Good
C2Y	32	0.376	0.521	17.2	1.38	Passable
C2X	24	0.562	0.712	14.2	1.26	Good
C2Z	32	0.382	0.492	18	1.28	Passable

4.*Invitro* drug release studies:

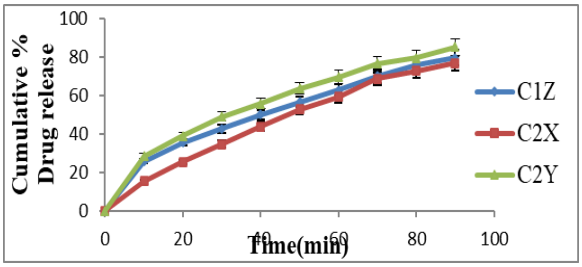


Fig:7 Graphical representation of cumulative percentage drug release of Felodipine (C1Z, C2X, C2Y)

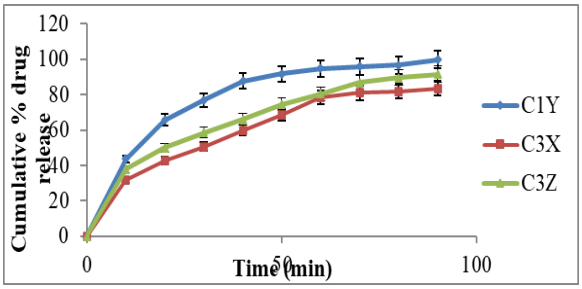


Fig:8 Graphical representation of cumulative percentage drug release of Felodipine (C1Y, C3X, C3Z)

Table 11

Time(min)	Cumulative percentage drug release					
	C1Z	C2X	C2Y	C1Y	C3X	C3Z
10	25.73±0.2	15.27±0.01	28.42±0.13	43.59±0.31	31.74±0.14	38±0.15
20	35.47±0.34	25.27±0.025	38.88±0.12	65.63±0.4	42.82±0.16	50.05±0.13
30	42.57±0.34	34.68±0.05	48.94±0.05	76.91±0.28	50.61±0.34	58.59±0.32
40	49.9±0.21	43.88±0.02	55.6±0.36	87.67±0.34	59.87±0.25	65.97±0.15
50	56.45±0.35	52.69±0.01	63.57±0.33	91.67±0.37	68.63±0.32	74.61±0.35
60	62.78±0.21	59.20±0.09	69.55±0.422	94.87±0.33	78.52±0.31	80.46±0.41
70	69.99±0.01	68.57±0.29	76.53±0.35	95.78±0.14	81.08±0.16	86.77±0.17
80	75.78±0.13	72.72±0.06	79.5±0.3	96.73±0.19	81.80±0.17	89.58±0.39
90	79.55±0.15	76.74±0.14	85.06±0.12	99.67±0.17	83.56±0.36	91.55±0.35

5.Particle size distribution, Zeta potential and Polydispersibility Index:

Tests	Formulation (C1Y)
Particle size	78.3 nm
Zeta potential	-17.4 mV
PDI	0.27
Self-emulsification time	47 sec

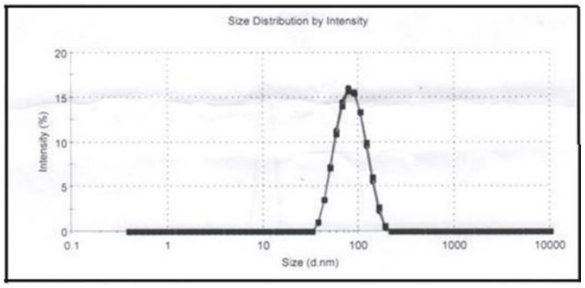


Fig 9: Particle size distribution:

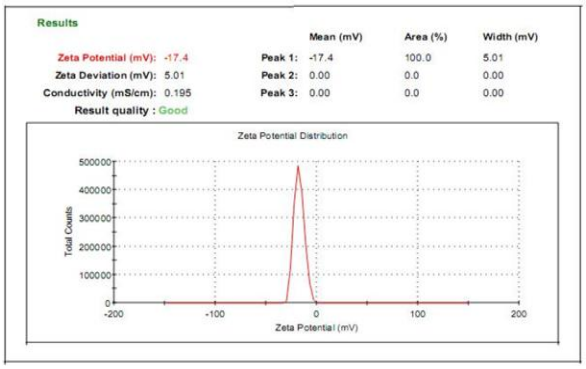


Fig 10: Zeta potential

IV. CONCLUSION

A particular self-micro emulsifying (SME) mixture comprising of clove oil, Tween20 and PEG 600 was selected and optimized for the purpose for delivering Felodipine. Four different formulations of different S/CoS ratio were prepared. Among these four prepared formulations of Liquid SMEDDS, formulation C1Y containing 7.5% oil, 61.7% surfactant and 30.8% co-surfactant was selected as optimized formulation. Optimized formulation converted into S-SMEDDS by adsorbing onto Aerosil 200 as carrier. Formulation C1Y had 78.3µm particle size and complete drug release in 90 minutes. In conclusion, Self micro emulsifying drug delivery systems were promising approach for the formulation of Felodipine. The oral delivery of hydrophobic drugs can be made possible by SMEDDS, which have been shown to improve oral bioavailability.

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