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[摘要] **目的** sirolimus SRL **方法**
SD IC SMEDDS NLC SRL SRL-SMEDDS SRL-NLC
SRL-SD SRL-IC 0.4%
SDS pH 1.2 pH 4.5 pH 6.8 pH 7.4 Rapamune®
结果 0.4% SDS 2 h
80% pH 1.2 SRL-SD IC SMEDDS NLC
SRL SRL-IC
SRL-SD SRL-IC SRL-NLC SRL-SMEDDS 9.1% 18.7% 33.2% 78.0% 97.6% **结**
论 SD SMEDDS NLC IC SRL SMEDDS SRL
[关键词]
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Study on sirolimus solubilization technology based on in vitro dissolution and in vivo bioavailability

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[Abstract] **Objective** To evaluate the effects of different solubilizing techniques on the in vitro dissolution and in vivo pharmacokinetics of Sirolimus (SRL). **Methods** Solid dispersions (SD), inclusion complex (IC), self-micro emulsifying drug delivery system (SMEDDS) and nano-structured lipid carrier (NLC) were selected as the solubilization technology for SRL. SRL-SMEDDS and SRL-NLC have obtained the optimal prescription in the previous studies. Additionally, the formulation process of SRL-SD and SRL-IC was screened by using inclusion rate and dissolution profiles as indicators. 0.4% SDS, water and buffer solutions with pH 1.2, 4.5, 6.8, 7.4 were used as dissolution media. The dissolution profile of the commercially available formulation Rapamune® and the lab-made solubilized preparations were investigated. The in vivo absorption of the above preparations was examined using a pharmacokinetic test in Beagle dogs. **Results** In 0.4% SDS, the dissolution of each preparation exceeded 80% in 2 h. In the medium of pH 1.2, the dissolution of SRL-SD could not be measured while the dissolution of IC, SMEDDS and NLC increased first and then decreased. In other media, the dissolution of the SRL was reduced. The SRL-IC showed the best dissolution without a significant decrease. The relative bioavailability of APIs, SRL-SD, SRL-IC, SRL-NLC and SRL-SMEDDS were 9.1%, 18.7%, 33.2%, 78.0%, and 97.6% respectively in vivo pharmacokinetic tests. **Conclusion** SD, SMEDDS, NLC, and IC can improve the in vitro dissolution and in vivo absorption of SRL. Among them, SMEDDS has the most significant improvement in the bioavailability of SRL.

[Key words] sirolimus solid dispersion inclusion complex SMEDDS nano-structured lipid carrier dissolution bioavailability

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sirolimus SRL
SRL
[1-4] SRL
CYP3A4
SRL
17% [5-7]
SRL
SRL self-
microemulsifying drug delivery system SMEDDS
solid dispersion SD
nanostructured lipid carriers NLC
SRL
SRL

1 仪器与试剂

1.1 仪器

Agilent 1200 Agilent
Starter 2C pH ()
RCZ-6BZ ()
()
NS1001L2K (NiroSoavi)
UV-2800AH ()
) - (AB-
SCIEX)

1.2 试剂

SRL (99.9%) SRL (3%
99.6%)
() Rapamune®(0.4%
) 6000(PEG 6000
PVP K30 - (Poloxamer 80
188) 35 (Cremophor EL
(Cremophor RH40
BASF (Labrafil
M1944CS) (Transcutol P) 80 SRL-SD
(Labrasol) - 0.4%
(Precirol ATO5)
(Gelucire 44/14) GATTEFOSSE

HP- -CD DM- -CD SBE- -CD(
)

2 方法

2.1 SRL 含量测定方法

HPLC
SRL [8] Eclipse XDB-C₁₈ 150 mm×
4.6 mm 5 μm - - 45 34
21 1 ml/min 278 nm
50 20 μl 2 4 8 12 16
20 μg/ml SRL
Y=54.712X+1.221 r=0.999 9 2~20 μg/ml

2.2 SRL 增溶方法

2.2.1 SRL-SMEDDS

[9] 1 g SRL
19 g Transcutol HP
22 g Labrafil M1944CS 39 g
Cremophor EL
SRL-SMEDDS

2.2.2 SRL-NLC

[10-11] Gelucire44/14 Crodamol
GTCC 75 SRL
-80
300 r/min 30 min
90 MPa 5
SRL-NLC SRL 0.21% Gelucire44/
14:Crodamol GTCC 1 2.1 10%
-80 7.33% SRL-NLC 42.6%
50% 4 1

2.2.3 SRL-SD

- SRL-SD
80 SRL
-18 4 h

80 SRL-SD
- 0.4%

SDS SRL-SD

2.2.4 SRL-IC

SRL
4 12 h SRL 4 h
SRL 0.22 μm
24 h
80 SRL-IC
SRL-IC 10 ml
50%
HPLC SRL
% = [SRL - SRL / SRL] × 100%

2.3 体外溶出试验

2015 0931
SRL
Rapamune® SRL-SMEDDS SRL-NLC SRL-IC SRL-SD
1 mg SRL
100 r/min 250 ml
0.4% SDS pH 1.2 pH 4.5
pH 6.8 pH 7.4
10 30 45 60 90 120 min
2 ml
HPLC

2.4 体内药代动力学试验

SRL Rapamune®
SRL-SMEDDS SRL-NLC SRL-IC SRL-SD
1 mg SRL
12 h 4 h
2 2
0.25 0.5 0.75 1 1.5 2 3 4 6 8 10 12 24
36 48 72 h
EDTA -20
[12]

3 结果

3.1 SRL-SD 的制备

3.1.1
1A SRL-SD
PEG6000>F68>PVP K30>HPMC606>HPMC-AS-

MF
50% SRL-SD
PEG6000 F68
[13] 3 1 2 1 1 1 1 2
1 3 PEG6000/F68 SRL
PEG6000/F68 2 1

1B
3.1.2 -
PEG6000/F68=2 1
SRL-SD -
PEG6000/F68 1 2 1 1 4 2
1 6 3 SRL-SD
2 h 100% 1C
- PEG6000/F68

3.2 SRL-IC 的制备

3.2.1 - HP- -CD SBE- -
CD DM- -CD SRL 11.21±
3.35 % 8.24±3.11 % 31.86±3.26 % 2A
DM- -CD SRL-IC
3.2.2 DM- -CD SRL-IC
2B
10 SRL-IC
30 50 P<0.01 58.61±4.16 %
10 SRL-IC

3.2.3 DM- -CD 200mg/ml 300mg/ml
SRL 52.12±4.17 % 58.61±
4.11 % P<0.05 2C DM- -CD
600 mg/ml P>0.05
DM- -CD 300 mg/ml
SRL-IC
3.2.4 0.5 ml 2 ml
2D 0.5 ml

SRL-IC
3.2.5 SRL 6 mg 8 mg
6 mg SRL 95.21±1.10 % 2E
SRL 6 mg
3.3 体外溶出度
SRL-SD SRL-IC SRL-SMEDDS SRL-

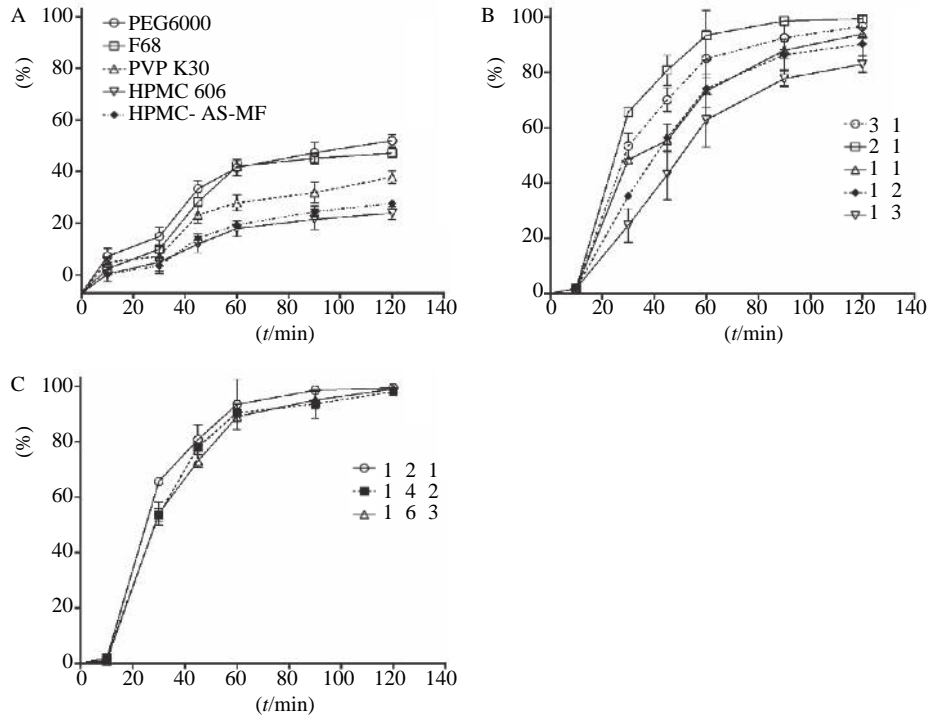


图1 单因素考察固体分散体的制备对体外溶出曲线的影响

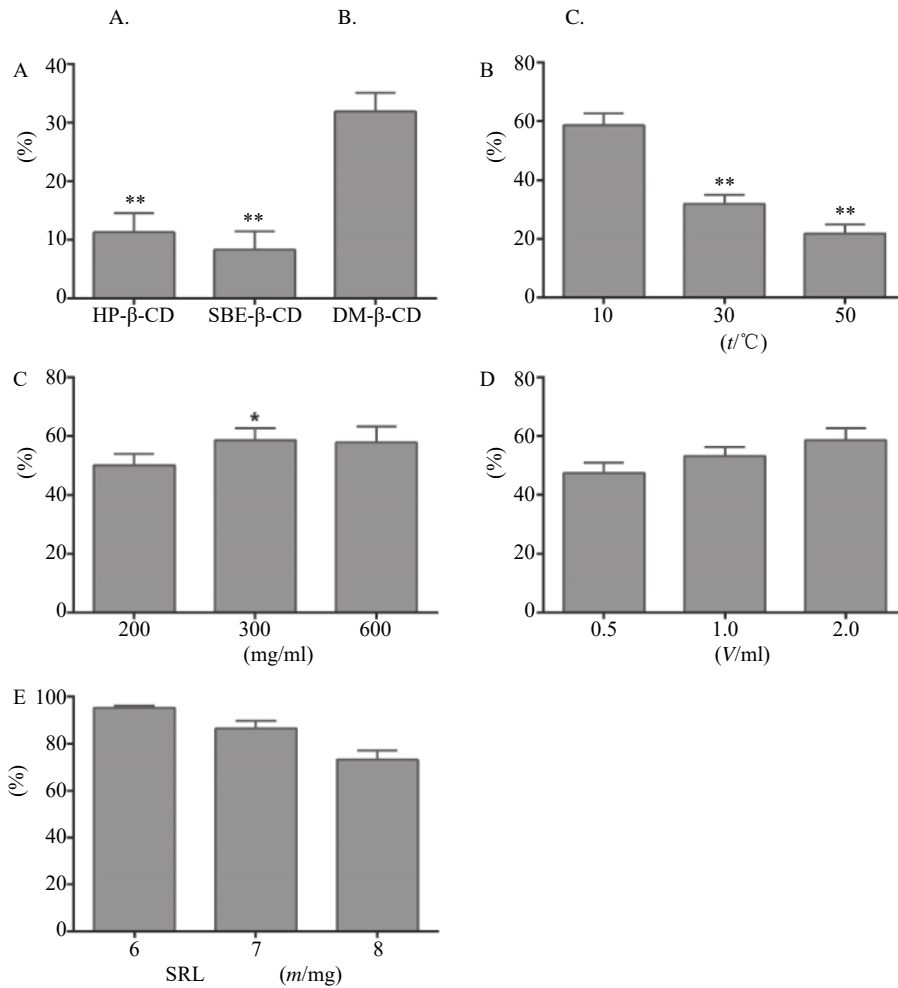


图2 单因素考察包合物的制备工艺对包合率的影响

A. - **P<0.01 DM-β-CD B. **P<0.01 10 C.
 *P<0.05 200 mg/ml D. E. SRL

NLC 3
 0.4% SDS 2 h 80%
 SMEDDS NLC 100%
 pH 6.8 SRL-SD 2 h
 65.00±4.90 % 76.70±1.95 %
 pH 4.5 pH 7.4 SRL-SD 1 h
 53.20±4.34 % 55.20±
 4.34 % pH 1.2
 SRL
 pH 4.5 pH 6.8 pH 7.4 SRL-IC
 40 min 2 h
 80% pH 1.2
 SRL-IC 30 min
 49.84±7.21 %
 SRL-SMEDDS SRL-NLC SRL-SD
 pH 6.8

0.4% SDS 80% pH 4.5 pH 7.4
 80%
 3.4 比格犬体内药动学试验
 SRL - 4 DAS
 3.2.6 1
 SRL-SD SRL-IC SRL-
 SMEDDS SRL-NLC Rapamune®
 332.8% 522.9% 1 228.6% 1 537.1%
 1 574.3% SRL
 Rapamune® SRL-
 SD SRL-IC SRL-NLC SRL-SMEDDS
 18.7% 33.2% 78.0% 97.6%
 SMEDDS SRL

4 讨论

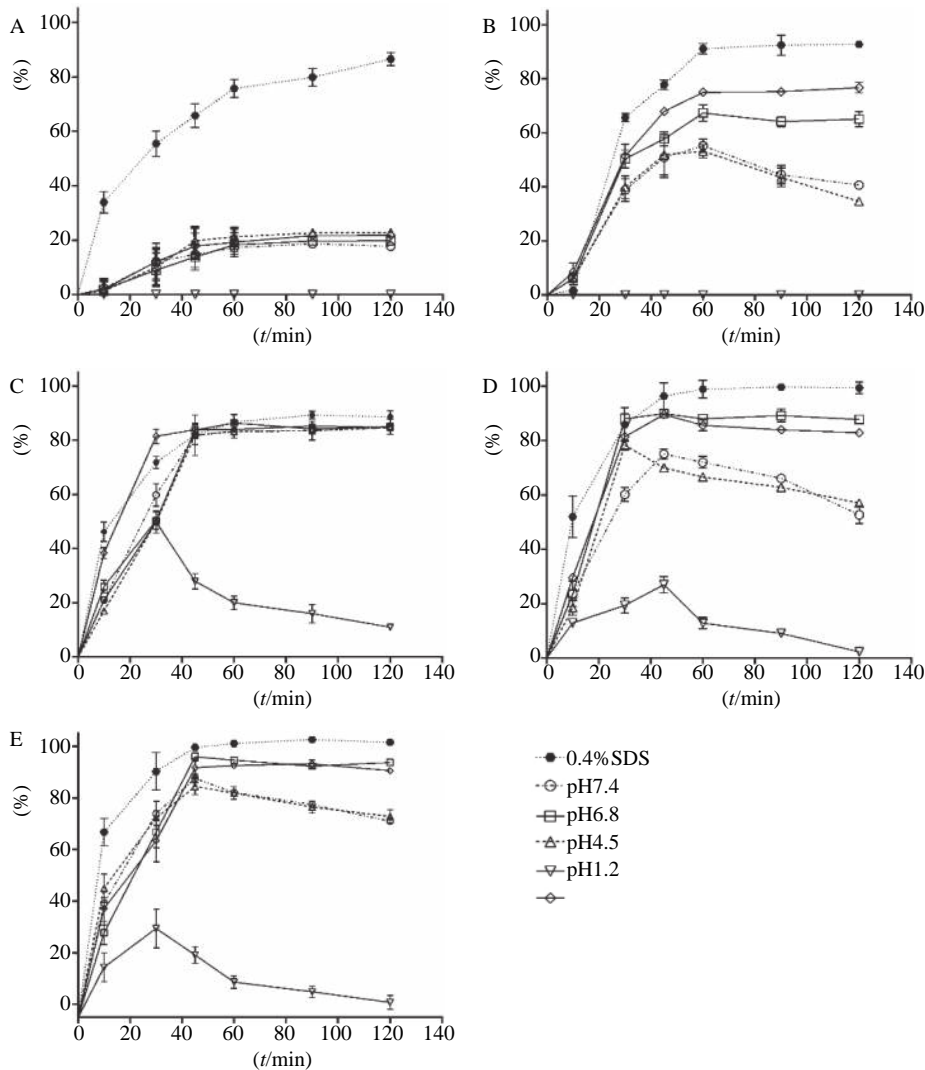


图 3 不同增溶制剂的西罗莫司在溶出介质中的溶出曲线图 (n=3)

A. Rapamune®; B. SRL-SD; C. SRL-IC; D. SRL-SMEDDS; E. SRL-NLC

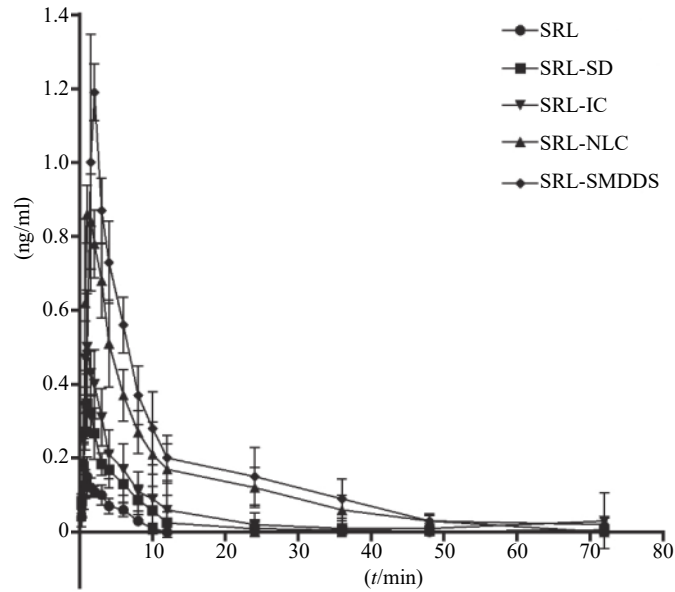


图 4 参比制剂与受试制剂平均血药浓度-时间曲线 (n=6)

表 1 非房室模型体内药动学参数 ($\bar{x} \pm s$)

	SRL	SRL-SD	SRL-IC	SRL-NLC	SRL-SMEDDS	Rapamune®
AUC ₀₋₇₂ (μg·h/ml)	0.70±0.13	2.06±0.79	3.66±2.64	8.60±2.03	10.76±1.57	11.02±2.73
AUC _{0-∞} (μg·h/ml)	0.73±0.15	2.07±0.81	3.78±2.84	8.67±1.95	11.15±2.11	11.75±3.13
t _{1/2} (t/h)	16.53±1.50	14.50±2.15	20.64±5.45	8.97±6.87	12.97±5.67	14.54±5.67
t _{max} (t/h)	1.04±0.25	1.25±0.28	1.04±0.25	1.13±0.31	1.50±0.38	1.83±0.26
c _{max} (ng/ml)	0.16±0.05	0.36±0.05	0.53±0.13	0.90±0.09	1.23±0.07	1.28±0.13

SRL 4

SRL SMEDDS Labrafil M1944 CS

SRL Cremophor EL^[9, 19-21] NLC

SRL CYP3A4 P

[14]

SRL [10-11]

CYP3A4 P

[15]

SRL [23]

SRL

SRL

SRL

[16-17]

pH SRL SMEDDS

NLC SRL

SD SRL

[18]

H⁺ OH⁻ SRL SRL

SRL

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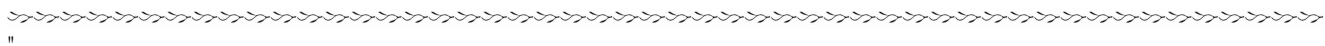
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QO" ."4234."53 7 4:3/4:60 hnc o o cvkqp 4237 5: 3 9:/: :0

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