



41 ??????????42 1.??  
43 ??????IVRT ?????????????  
44 ?????????????????????  
45 ?????????????????46 2.?  
47 ?IVRT????????????(??  
48 ???????????/????????/????) ?  
49 ???(? 0.45m ?)?????????1?  
50 IVRT????????????????  
51 ?????????????????  
52 ???IVRT????????????  
53 ?????????????????  
54 ??  
55 3.???  
56 ?????????????????  
57????????IVRT ?????????pH ???  
58 ??  
59 ?IVRT????????????  
60 ?????????????????  
61?????pH5 ~ 7 ???-????  
62 ?????????????????  
63 IVRT????????????  
64 ?????????????????  
65? (??) ?????? (r2?0.97)? ?????  
66 ?????IVRT ?????????  
67 ?????  
68 4.???  
69 ?????????IVRT????  
70 ???/ ?????????( Steady-StateRelease  
71 Kinetics)<sub>1</sub>????????  
72 ??????5 ?????????  
73 ?????(Steady-StateReleaseRates)????  
74 ???4 ?????????  
75 ?????????????(??<sub>76</sub> 30 ?????)????  
77 ?????????????78 ±15 ??±2% (?????)<sub>2</sub>?  
79 ?????????  
80 ?????????(±5%)??  
81 ?????????IVRT??  
82????????????83 (Pseudo-Infinite Dosing)<sub>3</sub>????  
84 ?????  
85 ?????????

86 ?????? (????? 600 rpm)<sub>1</sub>?<sub>87</sub> (?) IVRT ?????<sub>2</sub>?  
88 ??IVRT????????????????  
89 ?????????????????????  
90 ?????????????????IVRT ??????  
91 ??????  
92 ??????IVRT ?????????????  
93 ?????????????????<sub>94</sub> 1.????  
95 ?????????????????????  
96 ?????????????????????  
97 ?????????????????????(??<sub>98</sub> 32C±0.5C) ????? ?????????????  
99 ?????????±10%<sub>100</sub> 2.??  
101 IVRT????????????????  
102????(?? 32C±0.5C?????6 ??)????  
103 ?????????????????????  
104 ?????????  
105 ?????????????????  
106 ?????????????????????100%  
107 ± 5% ?  
108 3.????  
109 ?????????????????  
110 ?????????????????  
111 ?????????????????  
112 ?????? (?? ?????????????  
113 ??????????????????)<sub>114</sub> 4.????  
115 ?????????????????  
116 ??????????????????21C<sub>117</sub> ±2C?????50%RH±20%RH??  
118 5.????  
119 ?????????????????  
120 ??????????(?????????)?  
121 ??????????(r<sub>2</sub> ??0.97)????????  
122 ??????????IVRT ?????????  
123 ?????????????<sub>124</sub> 6.????  
125 ?????????(??) ??????  
126 ?????????????  
127 ?????????(%CV)????????(%CV)  
128 ??????15% ?????????/??/????/  
129 ?????????????  
130 ?????????  
131 7.???? (Dose Depletion)  
132 ?????????????



188 IVRT????????????????  
 189 ?????????????????????  
 190 ??????IVRT ?????????  
 191 ??????6 ??????????IVRT  
 192 ?????????????????????  
 193 ???(ABABAB?BABABA)?????194 (?) ??????????1?  
 195 ??????????????????( t1?  
 196 t2 ?)?????(?? μg/cm2 ??)?????  
 197 ??????????????????t ?  
 198 ?????????????????  
 199 ?????????????????  
 200 Mann-WhitneyU????????????  
 201 ??????(?) ?? 90%????  
 202 ??????????????203 (R)????????(T)???? R?  
 204 ?????????????????  
 205 ?????????(T)????????  
 206 ? (T) -?? (R) ?????????T/R ??????  
 207 ?????????TS ?????????RS ?  
 208 ?????????T/R ?????  
 209 ?1. ?????(TS)????(RS)?

|     | RS1     | RS2     | RS3     | RS4     | RS5     | RS6     |
|-----|---------|---------|---------|---------|---------|---------|
| TS1 | TS1/RS1 | TS1/RS2 | TS1/RS3 | TS1/RS4 | TS1/RS5 | TS1/RS6 |
| TS2 | TS2/RS1 | TS2/RS2 | TS2/RS3 | TS2/RS4 | TS2/RS5 | TS2/RS6 |
| TS3 | TS3/RS1 | TS3/RS2 | TS3/RS3 | TS3/RS4 | TS3/RS5 | TS3/RS6 |
| TS4 | TS4/RS1 | TS4/RS2 | TS4/RS3 | TS4/RS4 | TS4/RS5 | TS4/RS6 |
| TS5 | TS5/RS1 | TS5/RS2 | TS5/RS3 | TS5/RS4 | TS5/RS5 | TS5/RS6 |
| TS6 | TS6/RS1 | TS6/RS2 | TS6/RS3 | TS6/RS4 | TS6/RS5 | TS6/RS6 |

210????T/R ??????36 ?T/R ??????  
 211?????????8 ???29 ??????????  
 212 ??(?? 100)????? 90%?????????  
 213?????90%~111%?????????  
 214 ??????????????4 ?( 2 ??  
 215 ??2 ??????6 ???) ?? ??????  
 216?12 ??????????18 ?T/R ??????  
 217 ??????????324 ?T/R ?????????  
 218 ??????110 ???215 ?????(?????)  
 219 ??????90%?????????)? 90%~111%  
 220 ?????????????  
 221 ??????(IVPT)222 (?) IVPT ??????  
 223 IVPT????????????????

224 ??????????????????????  
225 ?????????????????IVPT ??????????  
226 ??????????????????????????????  
227 IVPT?????????????????????????  
228 ?????????????????  
229 IVPT?????(FluxProfiles)?????????230 (Pharmacokinetic Profiles)???? IVPT  
?????????  
231????????????????????(Cmax)???- ???  
232 ????(AUC)???IVPT????????????????  
233 ?????????????????????????????“?  
234 ????? (Cutaneous Pharmacokinetics)”????????“?  
235 ?????????????????????????” 4?  
236?????????????????????????????  
237 ??????????????????????????????  
238 ?IVPT ??????  
239 (?) IVPT ?????  
240 1.IVPT ??  
241 ??????IVPT ??????????????????  
242 ??????????????????????????????  
243 ?????????????  
244 2.IVPT ?????1,3,4?  
245 ?????????????/?????????????????  
246 ??????????????????????????????  
247 ?????????????(?? ?????????????????  
248 ??????) ?????????(?? ?????????????  
249 ??)?  
250 ??????????????????????????????  
251 ??????????????????????????????  
252?????????????????????????????????  
253 ??????????????????????????????  
254 ?????????????????????????32±0.5??  
255 ??????????????????????????????  
256 ?????????????IVPT????????????????  
257 ?(Non-Dermatomed)??? ?????????????/???  
258 ????  
259 3.IVPT ??????????  
260 ??????????????????????????????  
261 ??????????????????????????????  
262 ??????????????????????????????  
263 ?IVPT ??????????????????????????

264 ?????????????????????????????????/??  
265 ?????????????????????????????????  
266 ???.4?  
267 ?????????????????????????????  
268 ?????????????????????????????  
269 ?????????????????????????????  
270 ?????????????271 4.IVPT ?????4?  
272 ?????????pH ?????????????  
273 ?????????????????????  
274 ?????????????????????????  
275 ?????????????????????????  
276 ?????IVPT ?????????????  
277 ?????????????????????  
278 ?????????(?????)????  
279 ?????????(?? ??????)?  
280 ?????????????????????[???.0. 1%281 (w/v)? 0.2% (w/v) ]????20 ??(?? Oleth-20  
282 Volpo-20, ?Brij-20?CAS?9004-98-2) ?????  
283 ????????????????? (?????)  
284 ??????????)????????  
285 ????  
286 ?????????????(?? ? 0. 1%?  
287 ??????0.01% ??????)????  
288 ?????????/????  
289 ?????????????????290 5.IVPT ?????4?  
291 ?????????IVPT ?????  
292 ?????????????????  
293 ?????????(??) ???  
294 ?????????????  
295 ?????????????????8  
296 ?????  
297 ?????????????  
298 ?????????(??) ?????  
299 ?????????????  
300 ?????????????  
301 ?????????????  
302 ?????????????  
303 ?????????????IVPT ?????  
304 ?????????????????305 ????????????????????????????????? 306  
????????????????????????307 ?(±5%)???????????? 2~15mg/cm2 ??308 ?1?  
309 ?????????????????310 ??????(????? 600 rpm)?

311 ?????????????????????(4~6 ?)312 ??IVPT ?????????????????????4 ??313 ( ?  
314IVPT ?????????????????????315????????????????IVPT ?????????316 ???????  
1.????318 ?????????????????????319 ?????????????????????320?????????  
321 32C±0.5C)????? ??????????????????322 ???????????±10% ?323  
324 ?????????????????????325 ?????????????????????????  
326 ??????????  
327 3.?????????  
328 ?????????????????????????  
329????????????????????????  
330 ?????????????????????????  
331 ?????? (?? ??????????????????)  
332?????????????????????)?333 4.????  
334 ?????????????????????????  
335 ?????????????????????????21C 336 ±2C??????50%RH±20%RH??  
337 5.???????? (Permeation Profile and Range)  
338????????????????????????  
339 ??? (CumulativePermeation Profile)????????? 340 ( ??????????) ?????????????????  
341 ???  
342 6.?????????  
343????????????????????????  
344 ?????????????????????????  
345 ??????????????(%CV)????????? ??  
346 ??????  
347 ?????????????????????????  
348 ?????????????????????????  
349 ??????????????????????350 7.????  
351 ?????????????????????????  
352 ??IVPT????????????????????  
353 ?????????????????????(??  
354 ??????????????????????)?  
355 ?????????????????????10mg?????  
356 ??5% ?????????????????500?g????????  
357 ?48 ??IVPT?????????????????????35810?g?????500?g ?????????10?g?????????359 2%  
360 ?????????(?????????)  
361 8.???—?????????  
362????????????????IVPT ??????????  
363 ??????????4,?????????  
364 ?????IVPT????IVPT????????????“?  
365 ?????????????????????”?????????



366 ??????????IVPT ??????????????  
367 ??????“?????????”?????????????  
368 ??????????????IVPT?????????????  
369 ??????????????IVPT ??????????????  
370 ??????????????????????????????????  
371 ??????????????????????(???)???  
372 ????(Potency) ??????(?) ???????  
373 ???/?IVPT ?????/??????????????  
374 ???IVPT ???IVPT ??????????????  
375 ??????????????????????????????????  
376?????(?????????????????????????)?  
377 IVPT?????????????????????(? ? ? ?  
378 ???IVPT?)? ? ? ? IVPT ??????????  
379?????????????????????????????????  
380 ???<sub>4?</sub>?????????????IVPT ??????????  
381?????IVPT ?????????????????????(??<sub>382</sub> 4 ~ 6 ?????)???????????????? 4 ???  
383??????<sub>384</sub> 9.???  
385 ?????????(?? ??????) ????  
386 ??????????????????????????????????  
387 ??????????????????????????????????  
388 ??????????????????????????????????  
389?????IVPT ??????????????IVPT ??????<sub>390</sub> (?) ??????????  
391 ??????????????????????????????????  
392 ??????????????????????????????????  
393 ??????????????????????????????????  
394 ?????????????????????????????????<sub>395</sub> ( 6 ~ 8 ? ) ????????????? ICH M10 ??????  
396 ??????????????????????????????????  
397 (?) ?????? (????) ??????<sub>1?</sub>  
398 ??????????????????????????????????  
399 ????  
400????????????????????????????<sub>401</sub> (????????????????????????) ??????  
402 ??????????  
403 (?) IVPT ??????????<sub>4?</sub>  
404 ??????????????????????????IVPT ?  
405 ?????????????????????????????<sub>406</sub> 1.?????  
407 ??????????????????????????????????  
408 ?????????????<sub>409</sub> 2.???  
410 ??IVPT?????????????????????????  
411?????????????????????????????????  
412 ??????????????

413 3.??  
414 ?IVPT ??????????????????????415 (????) ??????????????????????  
416 ??????????????????????????????  
417?????

418a. ABABAB...

419 b. BABABA...

420 ????  
421 ?IVPT ??????????????????????  
422 ??????????????????????????????  
423 ??????????????????????????????  
424 ??????????????????????????????  
425 ?????????????IVPT ??????????????  
426 ??IVPT ??????????????????????????  
427 ??????????????????????????????  
428 ??????????????????????????????

429 ??????????430 4.IVPT ??

431IVPT?????????????????????????

432 ??????????????????????????????

433 ??(J)????????????? ??????????????

434 ??????????????

435 ??(?????) ??? Y-?????????

436 X-??????Y-??“J”??????/?/?/? (??ng/

437cm<sup>2</sup>/h)?????????????????????????

438?????????????????????????????

439 ??????????????????????(????/?/?

440 ?ng/ cm<sup>2</sup>)???? Y-????????X-??

441 ??????????????????????????

442 (?? 2.0 ng/mL)????????????????(??443 6.0 mL)????????????????????(??444 1 c  
)?????????????????????????

445 ?????? ?????????J ??????????

446  $J = [ (2.0 \text{ ng/mL}) \times (6.0 \text{ mL}) ] / ( 1 \text{ cm}^2 ) / (2 \text{ h}) = 447 \quad 6 \text{ ng/cm}^2/\text{h}$

448 ??????????????????????????????

449 ??????????????????????????????

450?????????2 ?????????????????????451 0 ?2 ?????????(?? 1 ??)?

452 ?????????????????????????(AMT)?

453 AMT ?????????????(????????????)?

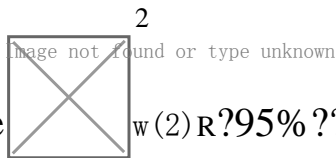
454 ??????????????????????????

455????????????????????(Jmax?????)

456????????)? AMT?????????????????

457????????????Cmax ?AUC ??????????

458????????(????????) ?????  
 459 ?????????  
 460 ?????IVPT?????(CI)?  
 461 a. ?????????(Jmax)  
 462 b. ????????? (AMT)  
 463 ?????IVPT????????  
 464????(????) ?????  
 465 ??4 ?????  
 466 ?IVPT ?????????  
 467 ?????????  
 468 ?????????/????  
 469????????  
 470 ???/?????????????????471 (?) ?????????4?  
 472 1.??SABE ( Scaled Average BE) ?????  
 473 ???IVPT ?????????  
 474 ?????????



475 a. (  $u_T$   $u_R$  ) ?  $e^{-\frac{2}{w(2)R}t}$  95% ?????  
 476 ??0 (????????)?  
 477b.  $T^2R$ ????????[1/m,m]????m=1.2500?  
 479 2.??ABE (Regular Average BE) ?????  
 480????IVPT ????? $u_T$  ?  $u_R$  ?90%??  
 481 ??[0.8000, 1.2500]????????  
 482 ?????  
 483 ?????

- 484 1. ???(USP)??<1724> Semisolid Drug Products
- 485 — Performance Tests.
- 486 2. FDA?In Vitro Release Test Studies for Topical Drug
- 487 Products Submitted in ANDAs. October 2022
- 488 3. EMA?Draft guideline on quality and equivalence of
- 489 topical products. October 2018
- 490 4. FDA: In Vitro Permeation Test Studies for Topical Drug
- 491 Products Submitted in ANDAs. October 2022
- 492 5. ?????(????)???

493 ?????( 2010 ?11  
 494 ?)  
 495 6. ?????  
 496???? (??)?( 2021 ?3 ? )

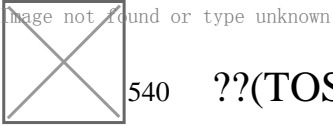
497 ???IVPT?????4?  
 498 ?????????(T)????(R)?  
 499 ?????????n ?????T ??  
 500  $j_{th}(j = 1, \dots, n) \text{ ??? } r_{jT} \text{ ?????????}$   
 501  $??R \text{ ??? } j_{th} (j = 1, \dots, n) \text{ ??? } r_{jR} \text{ ?????}$   
 502  $????(j) \text{ ???}(i) \text{ ?????????}$   
 503  $????$   
 504  $T_{ij} = \text{ ??? } j_{th} \text{ ??? } i_{th} \text{ ???}$   
 505  $IVPT \text{ ? } (J_{max} \text{ ? } AMT) \text{ ? } (i = 1, 2, \dots, r_{jT}, j = 1, 2, \dots, n)$   
 507  $R_{ij} = \text{ ???}(???) \text{ ? } j_{th} \text{ ??? } i_{th}$   
 508  $????IVPT \text{ ? } (J_{max} \text{ ? } AMT) \text{ ? } (i = 1, 2, \dots, r_{jR}, j = 1, 2, \dots, n)$   
 510  $r_{jT} = \text{ ??? } j_{th} \text{ ?????????} (j = 1, 2, \dots, n)$   
 512  $r_{jR} = \text{ ???}(???) \text{ ? } j_{th} \text{ ?????}$   
 513  $???? (j = 1, 2, \dots, n)$   
 514  $r^? = r_1(R) + r_2(R) + \dots + r_n(R) = R \text{ ?????}$   
 515  $n = \text{ ???}$   
 516  $????????T \text{ ? } R \text{ ? } n \text{ ?}$   
 517  $????????????????????$   
 518  $????????????????????$   
 519  $????????T = T_1(T) = T_2(T) = \dots = T_n(T) = T_1(R) = T_2(R) = \dots = T_n(R)$   
 521  $????????(????????)$   
 522  $????????) \text{ ? } (?? \text{ ?})$   
 523  $????????) \text{ ? } (?? \text{ ?})$   
 524  $????????) \text{ ? } (?? \text{ ?})$   
 525  $????????) \text{ ? } (?? \text{ ?})$   
 526  $????????) \text{ ? } (?? \text{ ?})$   
 527  $????????$   
 528  $????BE \text{ ? } (?? \text{ ?})$   
 529  $????????(T \text{ ? } R) \text{ ?}$   
 530  $????????3 \text{ ? } (?? \text{ ?})$   
 531  $??1$

532  $??IVPT??(J_{max} \text{ ? } AMT) \text{ ?}$   
 533  $??S_{wR} \text{ ?}$

534  $S_{wR} = \left( \begin{matrix} \text{Image not found or type unknown} \\ \text{Image not found or type unknown} \end{matrix} \right) 1/2$   
 535  $?? \begin{matrix} \text{Image not found or type unknown} \\ \text{Image not found or type unknown} \end{matrix} j = \begin{matrix} \text{Image not found or type unknown} \\ \text{Image not found or type unknown} \end{matrix} i(r) \begin{matrix} \text{Image not found or type unknown} \\ \text{Image not found or type unknown} \end{matrix} 1 R_{ij} \text{ ? } j \text{ ? } T_{jR}$   
 536  $????????$   
 537  $??S_{wR} \text{ ? } 0.294 \text{ ? } 2, 3.1 \text{ ? } 4.1 \text{ ?}$

538 ????????(SABE)????? IVPT ?????BE

539 ??SwR ?0.294?????2, 3.2 ?4.2?????T



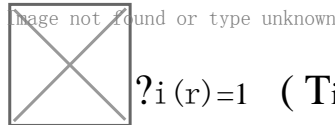
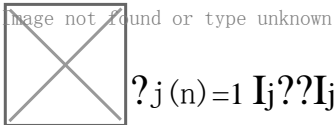
540 ??(TOST)?????????(ABE)????? IVPT

541 ?????BE

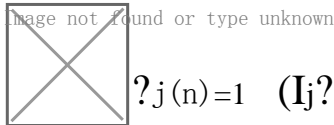
542 ??2

543 ??T ?R ?????????????(I?)????( se<sub>544</sub>( I?)) ?????? (df?)?

545 ??????????????????I? ?se ( I? ) df??



546 I? = I? = ?<sub>j(n)=1</sub> I<sub>j</sub>? I<sub>j</sub> = ?<sub>i(r)=1</sub> ( T<sub>ij</sub>? R<sub>ij</sub>)



547 S<sub>I(2)</sub> = ?<sub>j(n)=1</sub> (I<sub>j</sub>? I?)<sup>2</sup> (???????)

548 se(I?) = ?S<sub>I(2)</sub>/n

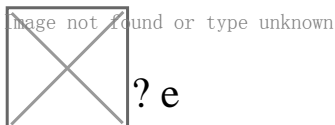
549 df? = n? 1

550 ???????????SAS?PROC MIXED(?

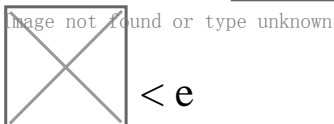
551 PROC GLM)?????I? ?se( I? ) df??

552 ??3.1 SABE ?

553 ?SABE ??????????



554 H<sub>0</sub>: ? e

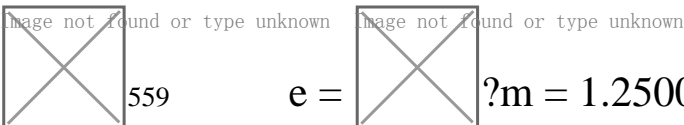


555 H<sub>a</sub>: < e

556 ???

557 u<sub>T</sub>? u<sub>R</sub> = T?R ??????????

558 G<sub>w(2)</sub>R = R ??????????



559 e = ?<sub>m</sub> = 1.2500 ( BE ??) , and G<sub>w0</sub> = 0.25<sub>560</sub> (?????)

561 ??????????????????????

562 ??Howe's Approximation (Howe, 1974) ( ? = 0.05 )?

2

563 ?? ( u<sub>T</sub>? u<sub>R</sub>) ? e G<sub>w(2)</sub>R ? ( 1-?) \*100% ????????

564 X + Y + sign(V) ? |V|<sup>1/2</sup>

565 ???

566 X = I?<sup>2</sup> ? se(I?)<sup>2</sup>

567 Y = ? e G<sub>w(2)</sub>R

568 X? = ( |I?| + t(1?a),df? ? se(I?) )

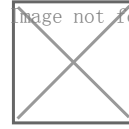
569 Y ? = ?e

Image not found or type unknown



570  $\text{sign}(V) = 1 \text{ if } V > 0; 0 \text{ if } V = 0; -1 \text{ if } V < 0$

Image not found or type unknown



571  $t_{(1-\alpha), df} \text{ Student's } t \text{ ( } 1 - \alpha \text{ ) } 100 \text{ X } t_{(1-\alpha), (r-n)}$

n) ??

573  $(1 - \alpha) 100$

574 3.2 ABE ?

575 ABE

576  $H_0: \mu_T = \mu_R \ln(m) \mu_T = \mu_R \ln(m)$

577  $H_a: \ln(m) < \mu_T = \mu_R < \ln(m)$

578 ??

579  $\mu_T = \mu_R = T \text{ R IVPT } 580$

581  $m = 1.2500 \text{ ( BE )}$

582  $\ln(m) \text{ BE }$

583

584  $\mu_T = \mu_R ( 1 - \alpha ) \times 100\%$

585  $I \pm t_{(1-\alpha), df} \text{ se}(I)$

586  $t_{(1-\alpha), df} \text{ ( } 1 - \alpha \text{ ) } 100$

587

588 4.1 SABC ( Scaled Average BE)

589 ??

590 IVPT

591

592 a.  $(\mu_T = \mu_R) \text{ e } G_{w(2)R} 95\%$

593  $0 \text{ ( } \text{ )}$

594 b.  $T \text{ R } [1/m, m] m = 1.2500$

596 4.2 ABC ( Regular Average BE)

597 ??

598 IVPT  $\mu_T = \mu_R 90\% [0.8000, 1.2500]$