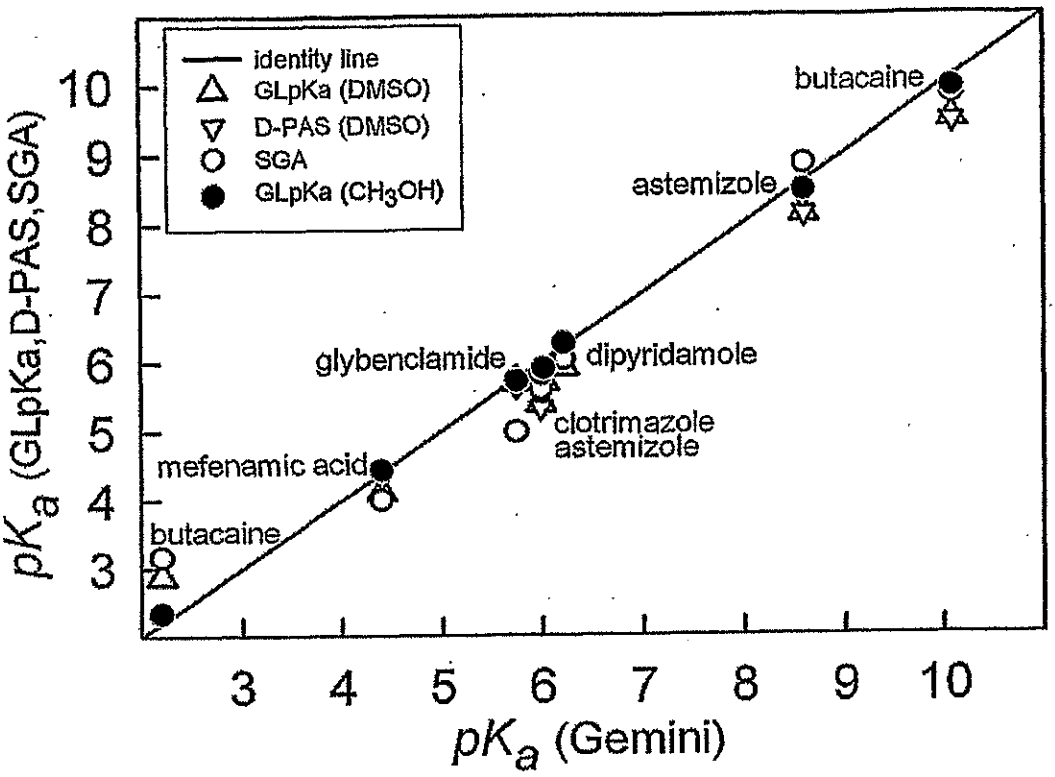

identity line
GLpKa (DMSO)
D-PAS (DMSO)
SGA
GLpKa (CH3OH)
butacaine
astemizole
glybenclamide
dipyridamole
clotrimazole
astemizole
mefenamic acid
butacaine
pKa (GLpKa,D-PAS,SGA)
pKa (Gemini)

Fig. 1

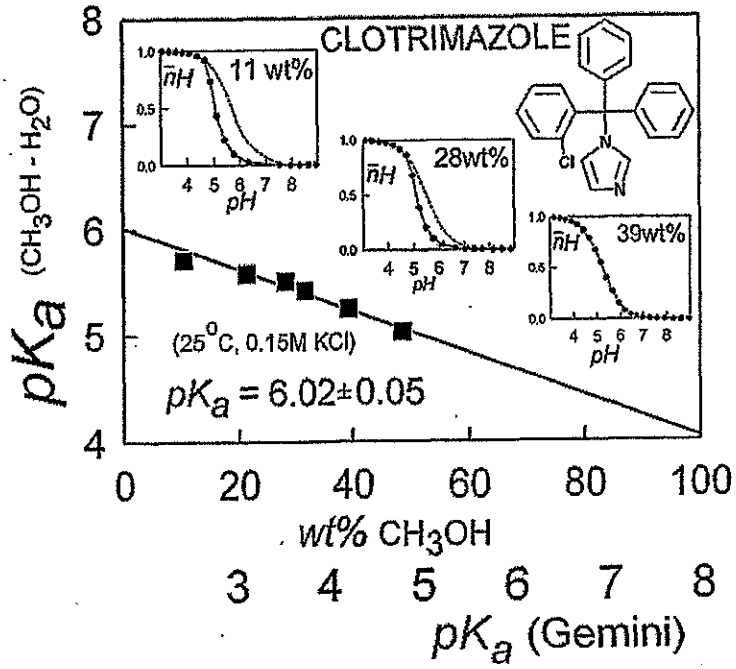

CLOTRIMAZOLE
11 wt%
28wt%
39wt%
nH
pH
(25°C, 0.15M KCl)
pKa = 6.02±0.05
pKa (CH3OH - H2O)
wt% CH3OH
pKa (Gemini)

Fig. 2

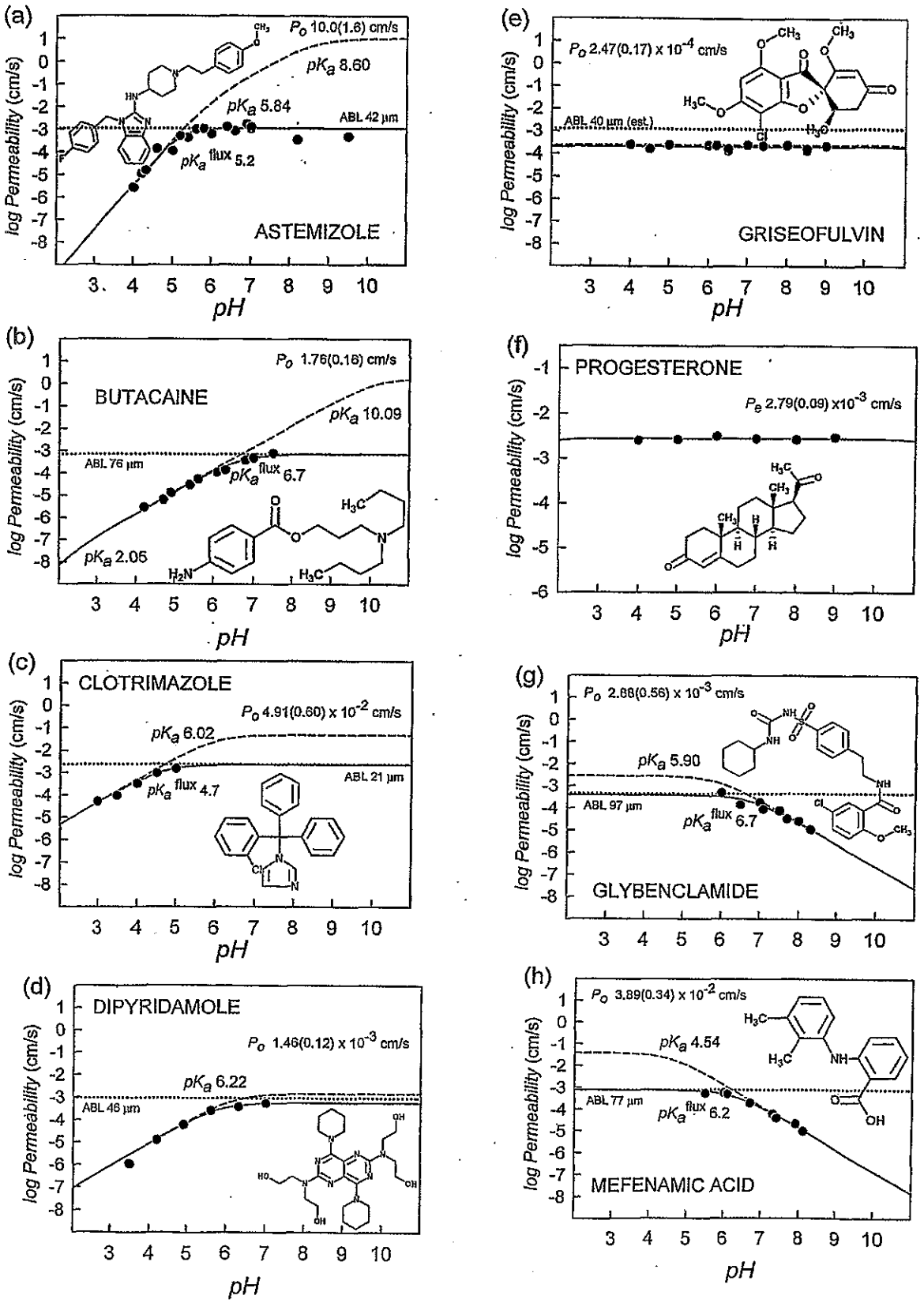

(a)
ASTEMIZOLE
P_o 10.0(1.6) cm/s
pK_a 8.60
pK_a 5.84
ABL 42 µm
pK_a flux 5.2
(b)
BUTACAINE
P_o 1.76(0.16) cm/s
pK_a 10.09
ABL 76 µm
pK_a flux 6.7
pK_a 2.05
(c)
CLOTRIMAZOLE
P_o 4.91(0.60) x 10^{-2} cm/s
pK_a 6.02
ABL 21 µm
pK_a flux 4.7
(d)
DIPYRIDAMOLE
P_o 1.46(0.12) x 10^{-3} cm/s
pK_a 6.22
ABL 46 µm
(e)
GRISEOFULVIN
P_o 2.47(0.17) x 10^{-4} cm/s
ABL 40 µm (est.)
(f)
PROGESTERONE
P_e 2.79(0.09) x10^{-3} cm/s
(g)
GLYBENCLAMIDE
P_o 2.88(0.56) x 10^{-3} cm/s
pK_a 5.90
ABL 97 µm
pK_a flux 6.7
(h)
MEFENAMIC ACID
P_o 3.89(0.34) x 10^{-2} cm/s
pK_a 4.54
ABL 77 µm
pK_a flux 6.2
log Permeability (cm/s)
pH

Fig. 3

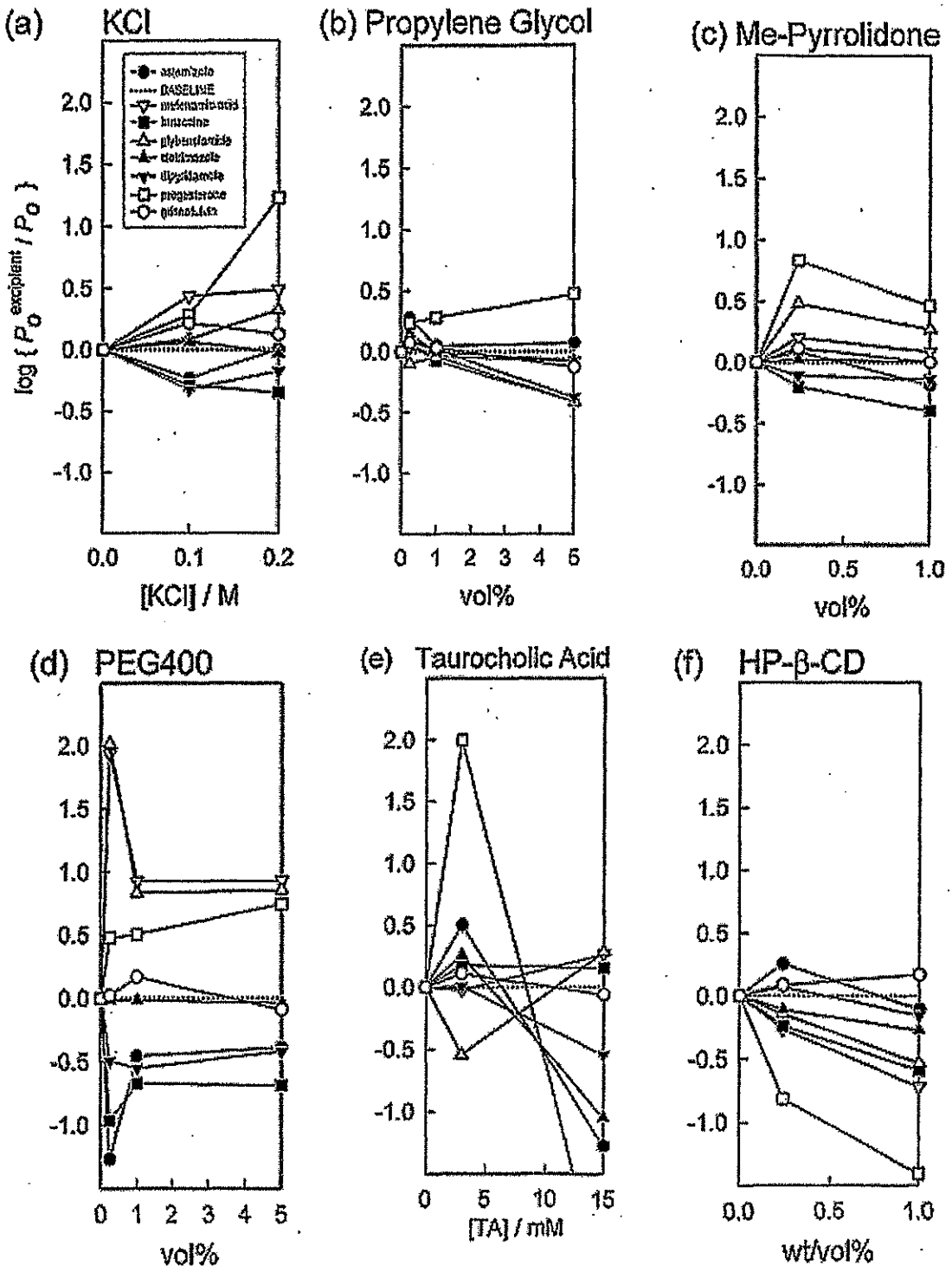

(a) KCl
(b) Propylene Glycol
(c) Me-Pyrrolidone
(d) PEG400
(e) Taurocholic Acid
(f) HP-β-CD
log { $P_o^{excipient}$ / P_o }
[KCl] / M
vol%
vol%
vol%
[TA] / mM
wt/vol%

Fig. 4



Fig. 5

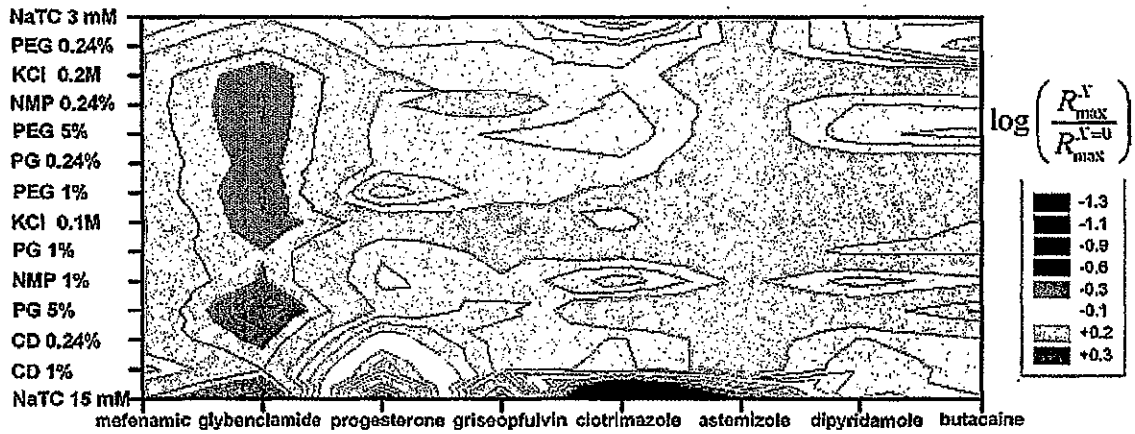


Fig. 6

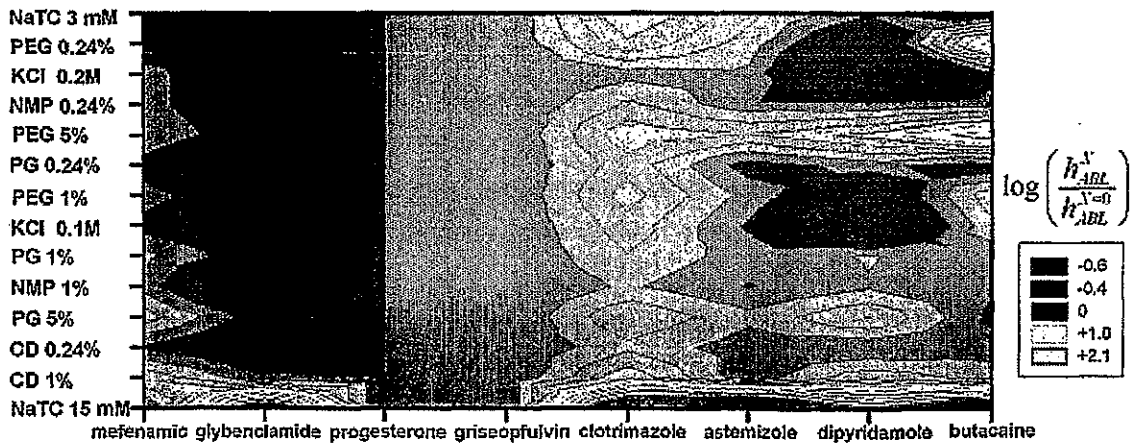


Fig. 7

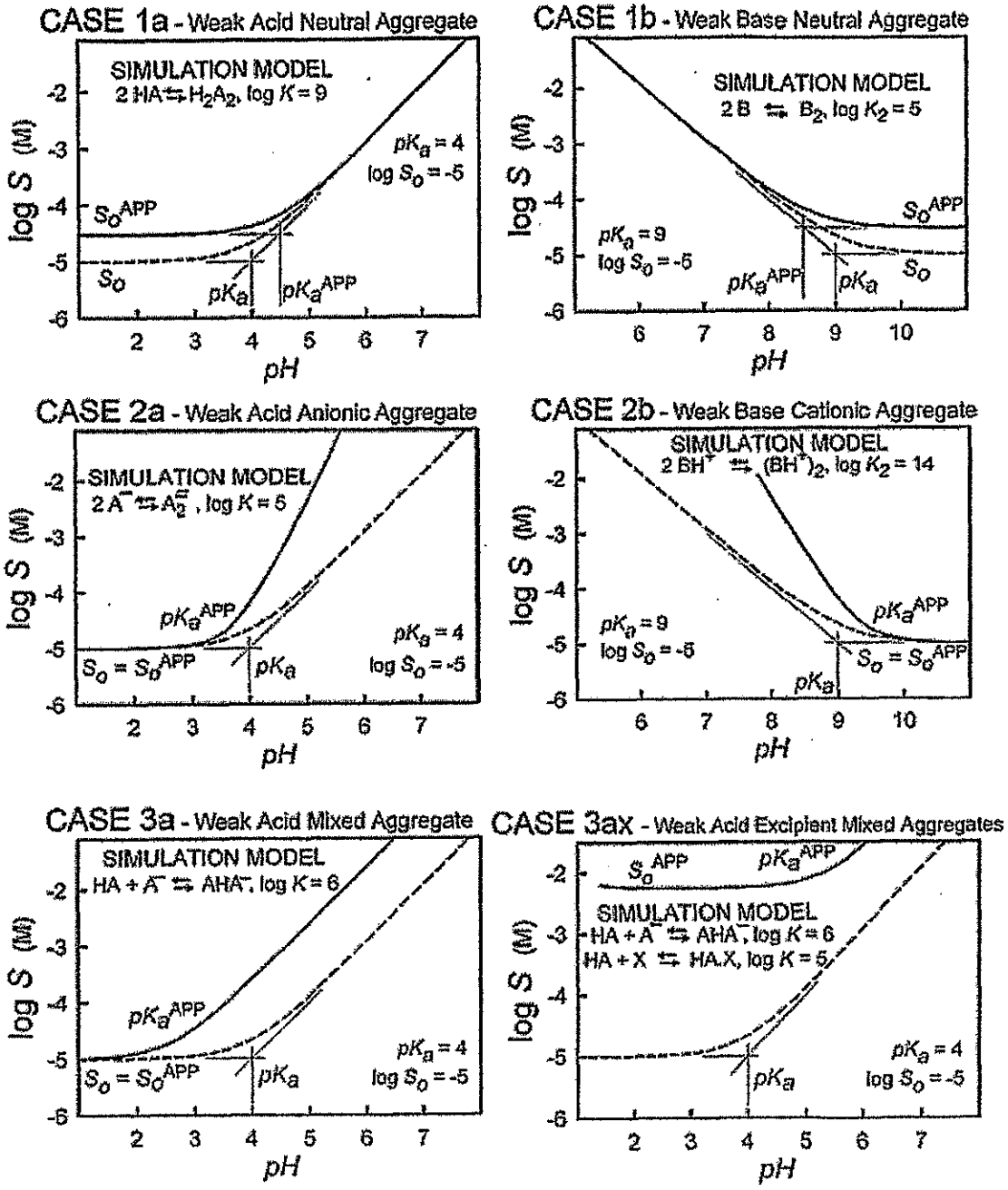

CASE 1a - Weak Acid Neutral Aggregate
SIMULATION MODEL
2 HA ⇆ H2A2, log K = 9
pKa = 4
log So = -5
So APP
So
pKa
pKa APP
log S (M)
pH
CASE 1b - Weak Base Neutral Aggregate
SIMULATION MODEL
2 B ⇆ B2, log K2 = 5
pKa = 9
log So = -5
So APP
pKa APP
pKa
So
log S (M)
pH
CASE 2a - Weak Acid Anionic Aggregate
SIMULATION MODEL
2 A⁻ ⇆ A2²⁻, log K = 5
pKa APP
So = So APP
pKa
pKa = 4
log So = -5
log S (M)
pH
CASE 2b - Weak Base Cationic Aggregate
SIMULATION MODEL
2 BH⁺ ⇆ (BH⁺)2, log K2 = 14
pKa = 9
log So = -5
pKa APP
So = So APP
pKa
log S (M)
pH
CASE 3a - Weak Acid Mixed Aggregate
SIMULATION MODEL
HA + A⁻ ⇆ AHA⁻, log K = 6
pKa APP
So = So APP
pKa
pKa = 4
log So = -5
log S (M)
pH
CASE 3ax - Weak Acid Excipient Mixed Aggregates
So APP
pKa APP
SIMULATION MODEL
HA + A⁻ ⇆ AHA⁻, log K = 6
HA + X ⇆ HA.X, log K = 5
pKa
pKa = 4
log So = -5
log S (M)
pH

Fig. 8

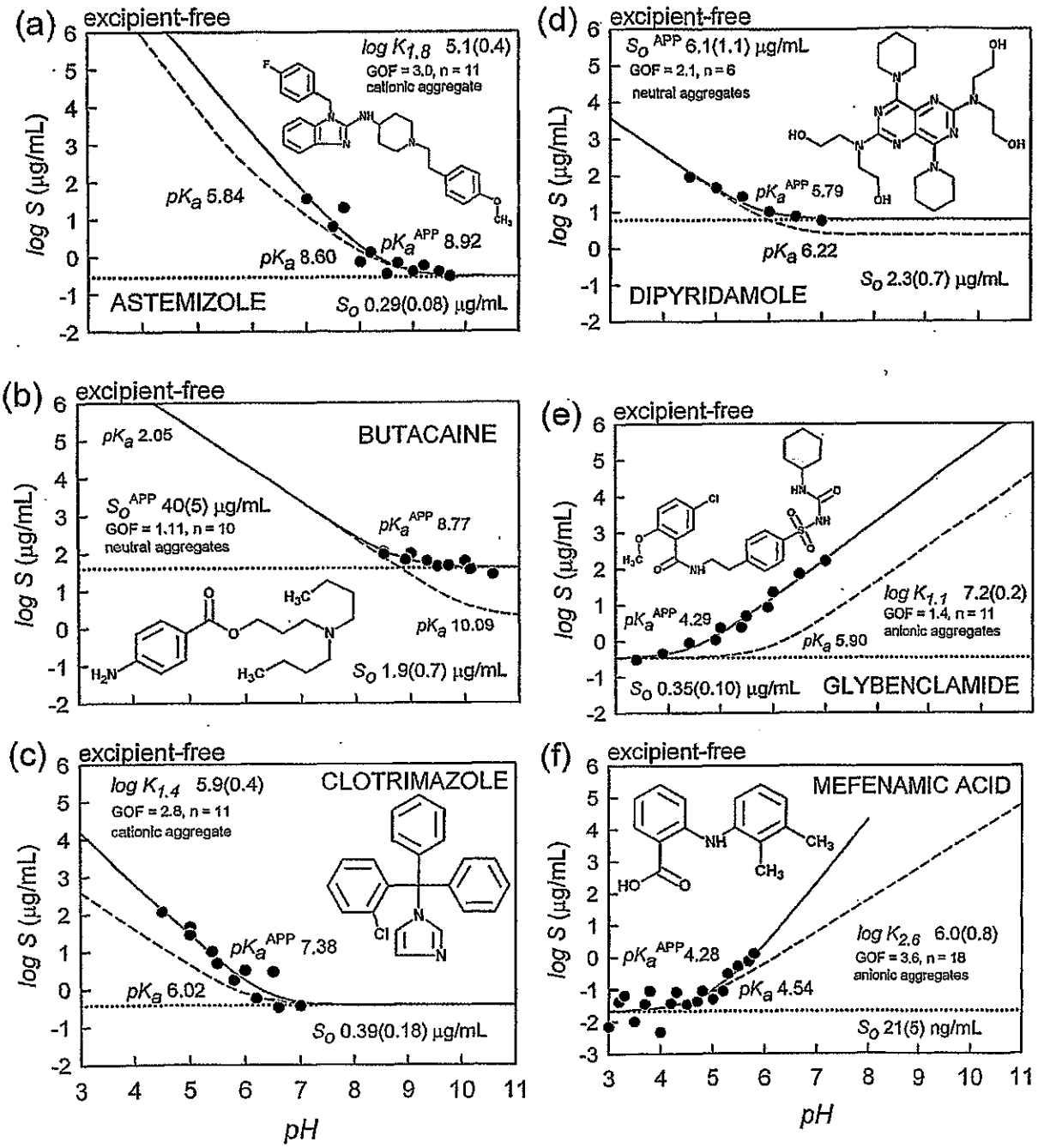

(a)
excipient-free
log K1,8 5.1(0.4)
GOF = 3.0, n = 11
cationic aggregate
pKa 5.84
pKa 8.60
pKa APP 8.92
ASTEMIZOLE
S0 0.29(0.08) µg/mL
(b)
excipient-free
pKa 2.05
BUTACAINE
S0 APP 40(5) µg/mL
GOF = 1.11, n = 10
neutral aggregates
pKa APP 8.77
pKa 10.09
S0 1.9(0.7) µg/mL
(c)
excipient-free
log K1,4 5.9(0.4)
GOF = 2.8, n = 11
cationic aggregate
CLOTRIMAZOLE
pKa APP 7.38
pKa 6.02
S0 0.39(0.18) µg/mL
(d)
excipient-free
S0 APP 6.1(1.1) µg/mL
GOF = 2.1, n = 6
neutral aggregates
pKa APP 5.79
pKa 6.22
DIPYRIDAMOLE
S0 2.3(0.7) µg/mL
(e)
excipient-free
log K1,1 7.2(0.2)
GOF = 1.4, n = 11
anionic aggregates
pKa APP 4.29
pKa 5.90
S0 0.35(0.10) µg/mL
GLYBENCLAMIDE
(f)
excipient-free
MEFENAMIC ACID
log K2,6 6.0(0.8)
GOF = 3.6, n = 18
anionic aggregates
pKa APP 4.28
pKa 4.54
S0 21(5) ng/mL
log S (µg/mL)
pH

Fig. 9

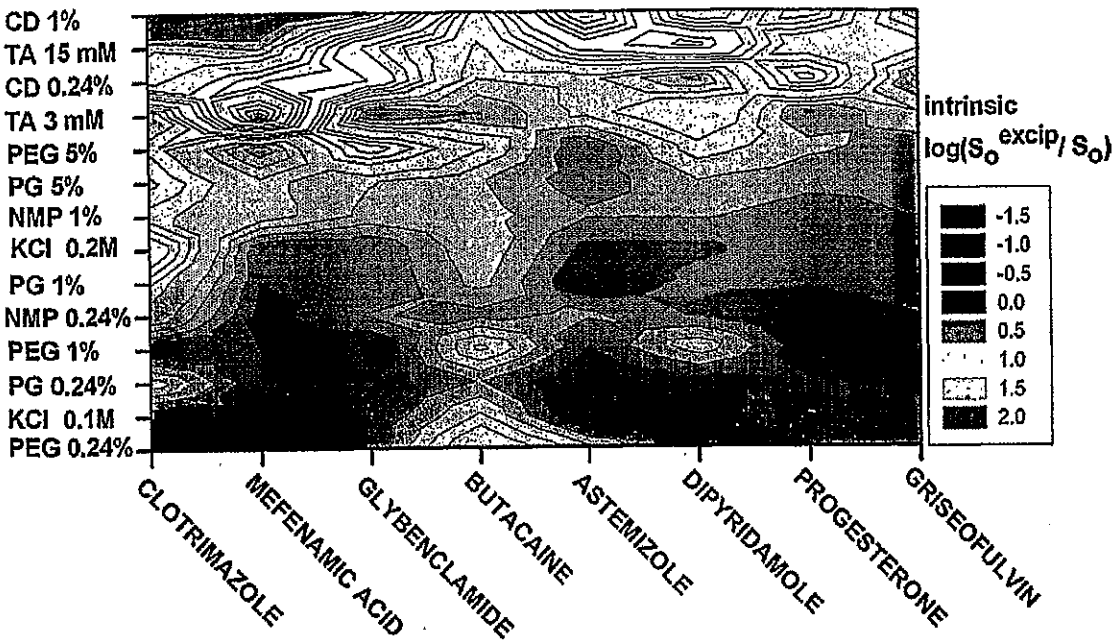

CD 1%
TA 15 mM
CD 0.24%
TA 3 mM
PEG 5%
PG 5%
NMP 1%
KCl 0.2M
PG 1%
NMP 0.24%
PEG 1%
PG 0.24%
KCl 0.1M
PEG 0.24%
intrinsic
log(S0 excip/ S0)
-1.5
-1.0
-0.5
0.0
0.5
1.0
1.5
2.0
CLOTRIMAZOLE
MEFENAMIC ACID
GLYBENCLAMIDE
BUTACAINE
ASTEMIZOLE
DIPYRIDAMOLE
PROGESTERONE
GRISEOFULVIN

Fig. 10

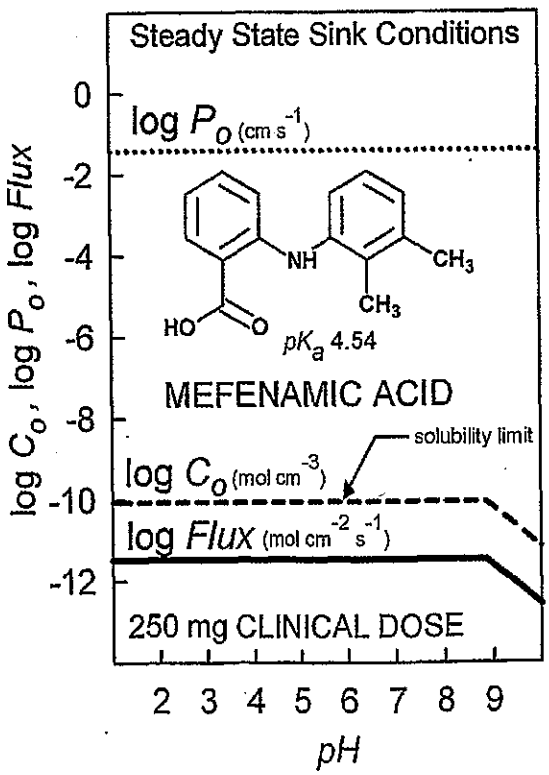

Steady State Sink Conditions
log Po (cm s-1)
NH
CH3
CH3
HO
O
pKa 4.54
MEFENAMIC ACID
solubility limit
log Co (mol cm-3)
log Flux (mol cm-2 s-1)
250 mg CLINICAL DOSE
log Co, log Po, log Flux
0
-2
-4
-6
-8
-10
-12
2 3 4 5 6 7 8 9
pH

Fig. 11

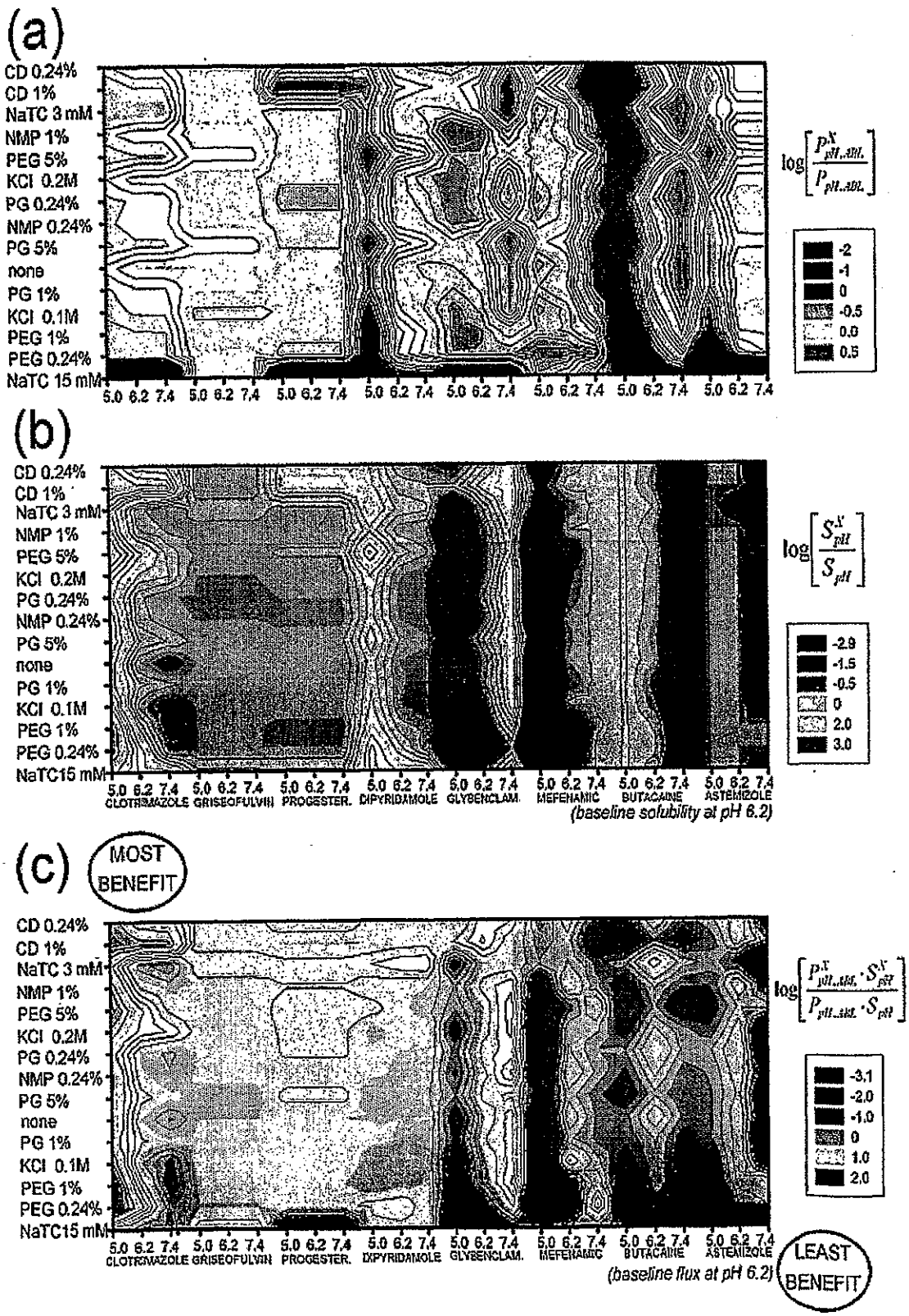

(a)
CD 0.24%
CD 1%
NaTC 3 mM
NMP 1%
PEG 5%
KCl 0.2M
PG 0.24%
NMP 0.24%
PG 5%
none
PG 1%
KCl 0.1M
PEG 1%
PEG 0.24%
NaTC 15 mM
5.0 6.2 7.4
-2
-1
0
-0.5
0.0
0.5
(b)
-2.9
-1.5
-0.5
0
2.0
3.0
CLOTRIMAZOLE
GRISEOFULVIN
PROGESTER.
DIPYRIDAMOLE
GLYBENCLAM.
MEFENAMIC
BUTACAINE
ASTEMIZOLE
(baseline solubility at pH 6.2)
(c)
MOST BENEFIT
-3.1
-2.0
-1.0
0
1.0
2.0
(baseline flux at pH 6.2)
LEAST BENEFIT

Fig. 12

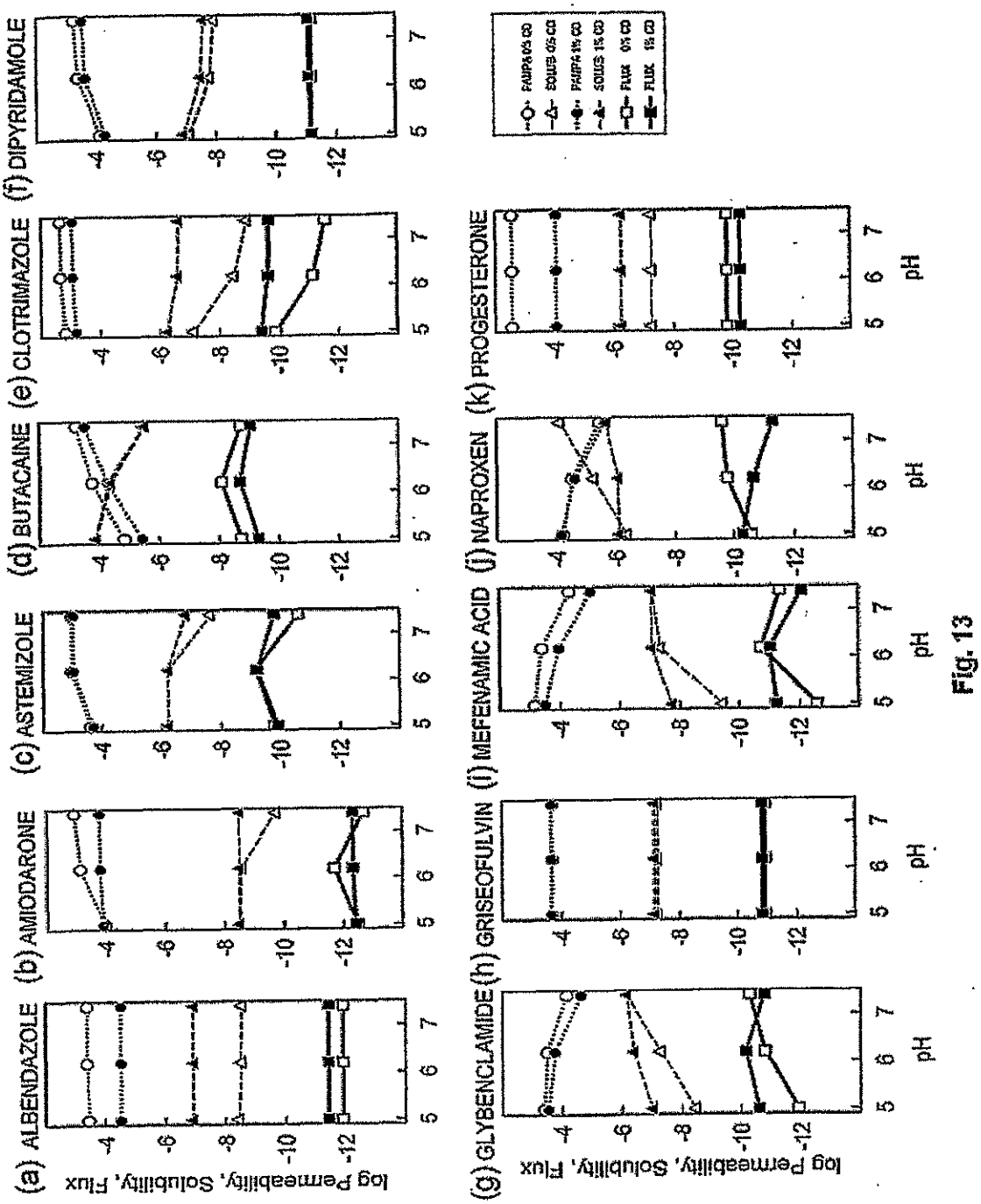

(a) ALBENDAZOLE
(b) AMIODARONE
(c) ASTEMIZOLE
(d) BUTACAINE
(e) CLOTRIMAZOLE
(f) DIPYRIDAMOLE
(g) GLYBENCLAMIDE
(h) GRISEOFULVIN
(i) MEFENAMIC ACID
(j) NAPROXEN
(k) PROGESTERONE
log Permeability, Solubility, Flux
pH
PAMPA 0.5 CD
SOLUS 0.5% CD
PAMPA 1% CD
SOLUS 1% CD
FLUX 0.5% CD
FLUX 1% CD

Fig. 13

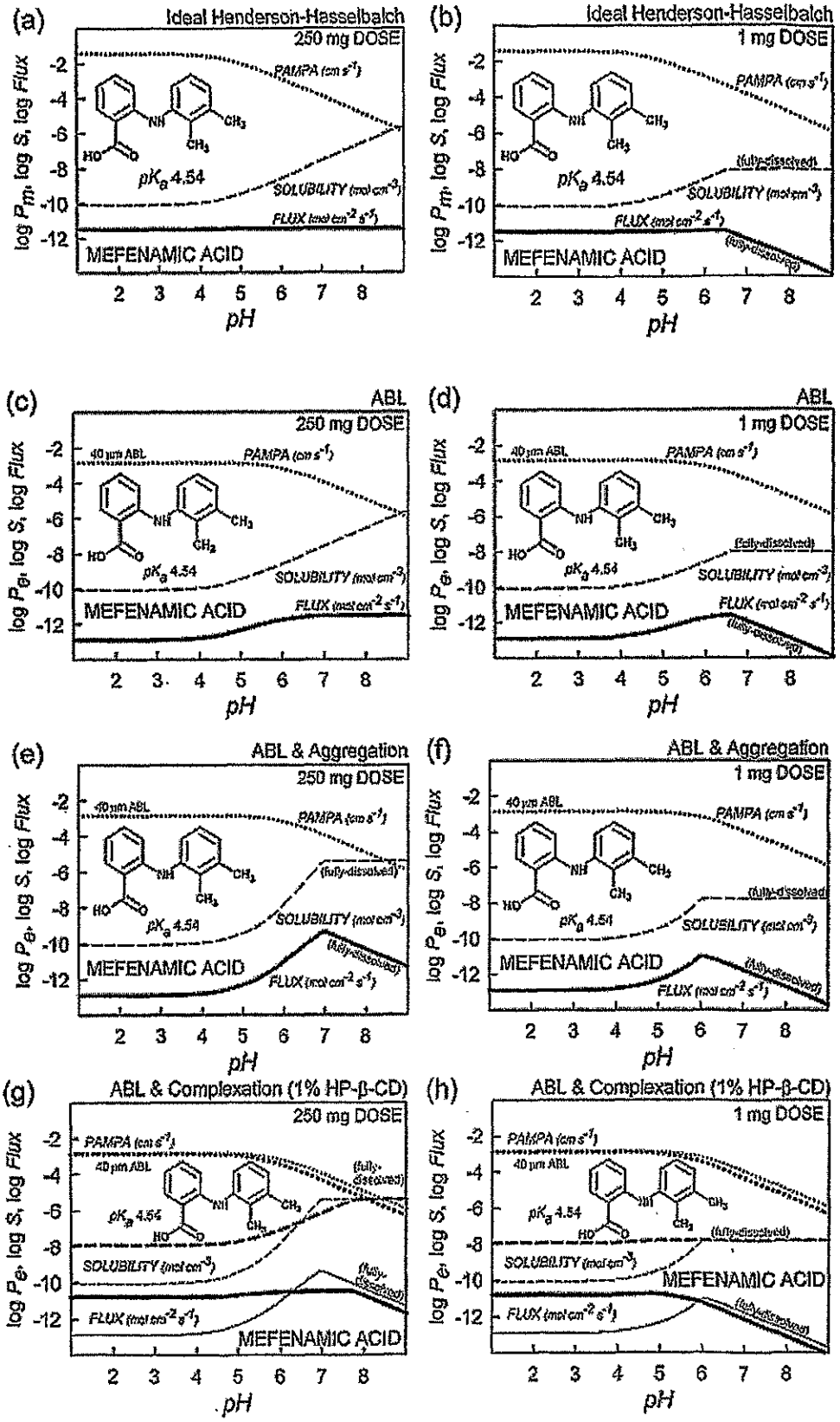

(a)
Ideal Henderson-Hasselbalch
250 mg DOSE
(b)
Ideal Henderson-Hasselbalch
1 mg DOSE
(c)
ABL
250 mg DOSE
(d)
ABL
1 mg DOSE
(e)
ABL & Aggregation
250 mg DOSE
(f)
ABL & Aggregation
1 mg DOSE
(g)
ABL & Complexation (1% HP-β-CD)
250 mg DOSE
(h)
ABL & Complexation (1% HP-β-CD)
1 mg DOSE
MEFENAMIC ACID
pKa 4.54
PAMPA (cm s-1)
SOLUBILITY (mol cm-3)
FLUX (mol cm-2 s-1)
40 µm ABL
(fully-dissolved)
log Pm, log S, log Flux
log Pe, log S, log Flux
pH

Fig. 14

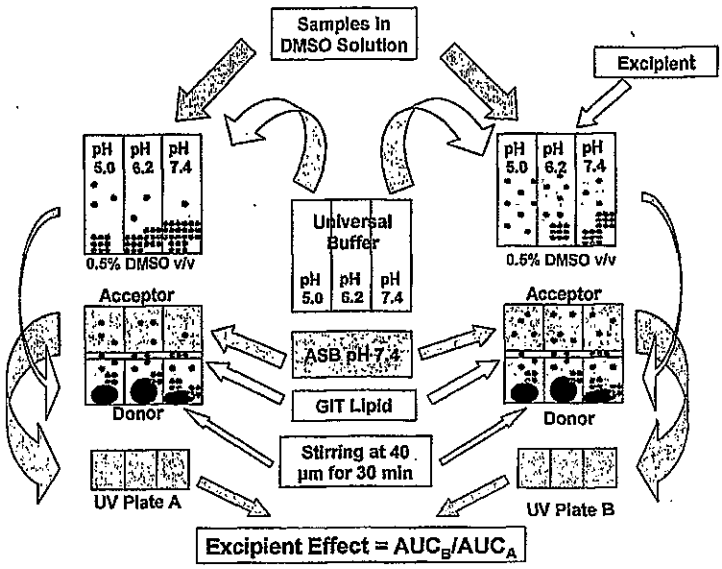

Samples in DMSO Solution
Excipient
pH 5.0
pH 6.2
pH 7.4
0.5% DMSO v/v
Universal Buffer
Acceptor
Donor
ASB pH 7.4
GIT Lipid
Stirring at 40 µm for 30 min
UV Plate A
UV Plate B
Excipient Effect = AUC$_B$/AUC$_A$

Fig. 15