ADDENDA

List of recent patents on selected drugs:

(1) Diacerein:

1. Chen, C. K., Lee, J. Y., Lu, W. S. & Brown, C. O. Methods for inhibiting expression of asc, expression of nlrp3, and/or formation of nlrp3 inflammasome complex using diacerein or its analogs. US 2017/0049733 A1 (2017).
2. Chen, C. K., Lee, J. Y., Lu, W. S. & Brown, C. O. Diacerein or rhein topical formulations and uses thereof. US 2017/0000732 A1 (2017).
3. Lim. H., Brown, C. O., Lu, W. S., Chung, T. K. & Chen, C. K. Formulations containing diacerein and methods of lowering blood levels of uric acid using the same. US 2016/0303050 A1 (2016).
4. Nakhat, P., Mandaogade, P., Jain, G. K. & Talwar, M. Self-emulsifying pharmaceutical compositions of rhein or diacerein. US 8,999,381 B2 (2015).
5. Cifter, U., Turkyilmaz, A. & Mutlu, O. Combined pharmaceutical formulation containing diacerein. US 2015/0004229 A1 (2015).
6. Cifter, U., Turkyilmaz, A., Akalin, N. P. & Zenginer, S. Formulations of flurbiprofen and diacerein. US 20140377343 A1 (2014).
7. Dabre, R., Jain, G. K., Estanove J. C., Pruvost, F., Sandal, R., Mandaogade, P. & Nakhat, P. Rhein or diacerein compositions. US 2014/0302126 A1 (2014).
8. Cifter, U., Turkyilmaz, A., Akalin, N. P. & Zenginer, S. & Mutlu, O. Combinations of diacerein and non-steroidal inflammation drugs. US 20140336148 A1 (2014).
9. Gao, D., Wu, J. S., Lu, W. S., Chen, S., Kuo, P. C. & Chen., C. M. Pharmaceutical compositions containing diacerein. US 20130156857 A1 (2013).
10. Ku, M. S., Chen, C. K., Lu, W. S. & Lin, I. Y. Methods and compositions for treating hyperuricemia and metabolic disorders associated with hyperuricemia. US 2012/0232044 A1 (2012).

(2) Febuxostat:

11. Dohnal, J., Kukackova, L. Formulations containing a solid solution of Febuxostat. EP3229782 A1 (Application-2017).
12. Kaushik, P., Thaimatam, R. & Prasad, M. Febuxostat solid dispersion. US 2015/0031732 A1 (2015).
13. Gujjar, C. Y., Rallabandi, B. R. C. & Patwari, P. S. Febuxostat Tablet. EP2902016 A1 (2015).
14. Srivastava, A., Das, S. N., Garg, M. K., Singla, A. K., Gupta, A. & Jadhav, P. A. Febuxostat Compositions. US 2014/0093563 A1 (2014).
15. Reddy, S. B., Suseendharnath, A., Madhavacharya, V., Vaya, N., Bhagwatwar, H. P. & Vobalabolna, V. Febuxostat Pharmaceutical Compositions. US 2014/0051733 A1 (2014).

Comparison of selected solubility enhancement approaches for each drug:

Table 1: Comparison of Pharmacokinetic parameters after oral administration of DAR-P, DAR-M, DAR-NS and DAR-IC in Albino rabbits.

Pharmacokinetic parameters*	**DAR-P**	**DAR-M**	**DAR-NS**	**DAR-IC**
C_{max} (µg/ml)	2.91±0.26	3.44±0.31†	8.54±0.23$^{\dagger\#}$	7.81±0.42$^{\dagger\#}$
T_{max} (h)	3.50±0.23	3.00±0.17†	2.00±0.14$^{\dagger\#}$	2.5±0.04$^{\dagger\#}$
AUC_{0-t} (µg*h/ml)	7.83±0.19	12.81±0.62†	30.90±0.56$^{\dagger\#}$	25.96±1.25$^{\dagger\#}$
$AUC_{0-\infty}$ (µg*h/ml)	8.09±0.36	13.19±0.91†	32.59±0.97$^{\dagger\#}$	27.02±1.74$^{\dagger\#}$
$AUMC_{total}$ ((µg*h^2/ml)	50.47±2.31	89.95±2.59†	227.45±4.87$^{\dagger\#}$	194.75±7.83$^{\dagger\#}$
MRT (h)	6.16±0.14	7.12±0.09†	7.06±0.10$^{\dagger\#}$	7.50±0.09$^{\dagger\#}$
$T_{1/2}$ (h)	7.94±0.42	10.65±0.57†	13.62±0.38$^{\dagger\#}$	10.21±0.26$^{\dagger\#}$
$K_{elimination}$ (h^{-1})	0.12±0.02	0.07±0.01†	0.05±0.01$^{\dagger\#}$	0.07±0.01$^{\dagger\#}$
F (%) w.r.t DAR-P	100	163.60†	394.64$^{\dagger\#}$	331.55$^{\dagger\#}$

***** Data are shown as Mean±SD, n=3, †P<0.05 compared with DAR-P, $^{\#}$P<0.05 compared with DAR-M.

By observing the pharmacokinetic parameters (Table 1) of DAR-P, DAR-M, DAR-NS and DAR-IC in Albino rabbits, it can be concluded that **DAR-NS was better than DAR-IC as DAR-NS was showing higher AUC and F (%) values**.

Table 2: Comparision of Pharmacokinetic parameters after oral administration of FBX-P, FBX-M, FBX-NS and FBX-IC in Albino rabbits.

Pharmacokinetic parameters*	**FBX-P**	**FBX-M**	**FBX-NS**	**FBX-IC**
C_{max} (µg/ml)	16.25±0.51	18.76±0.25	48.71±0.46$^{\dagger\#}$	42.98±0.95$^{\dagger\#}$
T_{max} (h)	1	1	0.5$^{\dagger\#}$	0.75$^{\dagger\#}$
AUC_{0-t} (µg*h/ml)	84.30±1.35	113.14±4.12	218.26±4.86$^{\dagger\#}$	259.89±9.42$^{\dagger\#}$
$AUC_{0-\infty}$ (µg*h/ml)	94.37±2.14	138.02±6.18	226.17±5.32$^{\dagger\#}$	272.51±12.05$^{\dagger\#}$
$AUMC_{total}$ ((µg*h^2/ml)	760.75±9.24	1076.82±9.85	1769.39±21.35$^{\dagger\#}$	2383.25±41.57$^{\dagger\#}$
MRT (h)	9.02±0.22	9.52±0.39	8.11±0.98$^{\dagger\#}$	8.77±0.29$^{\dagger\#}$
$T_{1/2}$ (h)	14.58±0.29	16.32±0.18	12.59±0.62$^{\dagger\#}$	12.04±0.34$^{\dagger\#}$
$K_{elimination}$ (h^{-1})	0.05±0.01	0.04±0.01	0.06±0.01$^{\dagger\#}$	0.06±0.01$^{\dagger\#}$
F (%) w.r.t FBX-P	100	134.21	258.91$^{\dagger\#}$	308.29$^{\dagger\#}$

***** Data are shown as Mean±SD, n=3, †P<0.05 compared with FBX-P, $^{\#}$P<0.05 compared with FBX-M.

In case of FBX, although FBX-NS was having higher C_{max} than FBX-IC but FBX-IC was found better than FBX-NS on the basis of higher AUC and F (%) values.

The developed formulations were subjected to in vitro and in vivo evaluation and found to be superior to the available marketed formulations of respective drugs. The studies revealed that the developed formulation were less toxic, more permeable and more bioavailable than the existing marketed formulations hence can be served as an alternative to the existing one.