International Journal of ChemTech Research
CODEN (USA): IJCRGG ISSN : 0974-4290
Vol.6, No.3, pp 1800-1802, May-June 2014

ICMCT-2014 [10th – 12th March 2014]
International Conference on Materials and Characterization Techniques

# Interdisciplinary Approach to Nano – crystalline Active Pharmaceutical Ingredients: a Brief Review

**M. J. Joshi***

***Crystal Growth Laboratory, Department of Physics, Saurashtra University, Rajkot 360 005, Gujarat, India**

***Corres. author :mshilp24@rediffmail.com**

**Abstract:** The number of poorly soluble drugs and drug candidates (new chemical compounds) is rapidly increasing. The solution has come by developing nano crystals to increase drug solubility and dissolution velocity, which needs interdisciplinary approach. In the present review the importance of nano crystals of Active Pharmaceutical Ingradients (API) is briefly covered by considering two API molecules,i.e., n-Butyl 4-(3, 4-dimethoxyphenyl)–6–methyl–2–thioxo–1,2,3,4 tetrahydropyrimidine–5–carboxylate and 1-phenyl-3-(propan-2-yl)-1H-pyrazol-5-ol as model candidates. These nano particles were synthesized by water-oil micro-emulsion technique and characterized by Powder XRD, TEM, FTIR and thermal analysis.
**Keywords:** Nano – crystalline, Active Pharmaceutical Ingredients, Interdisciplinary Approach.

## Introduction:

As per one estimate nearly 70% of molecules developed as drug candidates have solubility problems and face poor oral bioavailability and delivery problems. The solution of the problem came in terms of nano crystals to increase drug solubility and dissolution velocity in early 1990s. The first nano formulation drug was marketed in the year 2000 as Rapamune®. Reducing the particle size of an Active Pharmaceutical Ingredient (API) is a reliable technique of improving the bioavailability of relatively insoluble drugs[1]. Altogether, the nanotechnology is effectively employed in medicine to achieve the targeted drug delivery, encapsulation of API, altered dosages, etc. [2].

The market survey indicates the growth of nano pharmaceuticals from $406 million in 2004 to $16.6 billion in 2014.The nano particles for pharmaceutical applications have advantages such as macrophage evasion, ease to cross blood-brain barrier, readily slip through cell junction, easy to bio-integrate, deliver large aliquots and enhance permeation and retention [3].Nano-particles can efficiently deliver conventional drugs, recombinant, proteins, vaccines and nucleotides evenfor tissue or cell specific targeting of drugs and the reduction of unwanted side effects by a controlled release. This has been by Kayser *et al.* [4].Pharmaceutical companies are applying nanotechnology to enhance or supplement drug target discovery and drug formulation.This encourages interdisciplinary approach.

Pyrimidine and Pyrazole based compounds find many pharmaceutical applications [5, 6]. In the present paper, the nano particles of two different active pharmaceutical ingradient (API) molecules, i.e., n-Butyl 4-(3, 4-dimethoxyphenyl)–6–methyl–2–thioxo–1,2,3,4 tetrahydropyrimidine–5–carboxylate( abbreviated

as n-butyl THPM) and 1-phenyl-3-(propan-2-yl)-1H-pyrazol-5-ol (abbreviated as PPHP) shown in figure 1 (a, b), are briefly reviewed as model candidates.

## Experimental:

The n-butyl THPM and PPHP nano-crystalline particles were synthesized by using water/oil (w/o) micro-emulsion technique. Micro-emulsions are isotropic, transparent and thermodynamically stable systems composed of water, oil and surfactant; which find large number of applications [7]. The synthesis of nano particles of n-butyl THPM was carried out using micro-emulsion of water, Triton X-100 surfactant and n-butanol; while for the synthesis of PPHP nano particles the micro-emulsion consisting of water, Triton X-100 surfactant and n-heptane was used. This has been discussed in detail elsewhere [8, 9]. Figure 2 shows the TEM image of synthesized nano particles of n-butyl THPM, which exhibits spherical morphology. The nano particles of PPHP were also having spherical morphology.The samples were characterized by powder XRD, TEM, FTIR and TG – DTA – DSC.

### Results and Discussion:

The powder XRD studies indicated the characteristic peak broadening due to nano crystalline nature. The crystal structure remained the same as those for the bulk crystalline materials [9]. The results are summarized in table 1.

**Table 1 Unite cell parameter and crystallite size of n- butyl THPM and PPHP**

| sample | Unit cell parameters | | | | | | Average crystallite size nm |
|---|---|---|---|---|---|---|---|
| | a (Å) | b (Å) | c (Å) | α | β | γ | |
| n-butyl THPM | 7.1980 | 10.3378 | 10.2246 | 103. 78$^0$ | 107. 56$^0$ | 92.66 $^o$ | 35.00 |
| PPHP | 11.1593 | 11.2247 | 14.1140 | 73.333$^o$ | 88.286$^o$ | 82.767$^o$ | 33.00 |

The FTIR spectra were recorded for both nano particles indicated the presence of characteristic functional groups and the spectra were matching with those of bulk crystalline materials. The spectra also indicated the absence of surfactant as well as oil phase used during the synthesis of nano particles by micro-emulsion [9]. The FTIR spectra were again taken after the period of six months to assess the stability of the synthesized nano particles and were found to be the same as earlier.

Figure 3 shows the TG plot of nano n – butyl THPM. The sample remains stable up to 150 $^o$C and then slowly starts decomposing and beyond 260$^0$ C starts decomposing rapidly. The complete decomposition takes place within 630 $^o$C. In figure 3 a minor weight loss of the order of 0.2 percent of weight is observed within 160 $^o$C - 180 $^o$C, which corresponds to a sharp endothermal peak at 177.5 $^o$C with 102.62 J/g enthalpy due to phase change such as melting. This endothermic peak is comparatively small in crystalline sample. The sample then remains almost stable up to 250 $^o$C with 0.05 percent weight loss. A broad exothermic peak at 540.3 $^o$Cis due to the combustion of organic compounds. Thermal study suggests slightly high thermal stability of the nano particles with comparison to bulk crystalline samples [9]. The PPHP nano particles remained stable up to 168 $^o$ C and then the decomposition took place [9]. With comparison to the bulk crystalline samples, the nano crystalline particles exhibited slightly more thermal stability. This might be due to high surface energy as result of contraction of surface bonds giving slightly more thermal stability then the bulk samples. The thermal analysis was repeated on samples after six months and gave the same results indicating good thermal stability under atmospheric conditions.

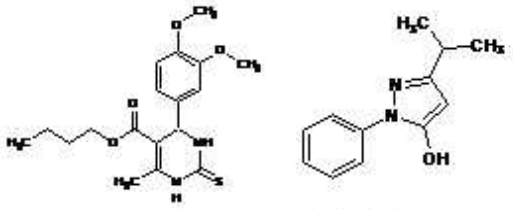

Figure 1 Structure of(a) n-butyl THPM (b) PPHM

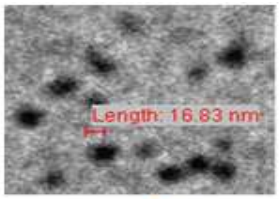


Figure 2 TEM image of n-butly THM

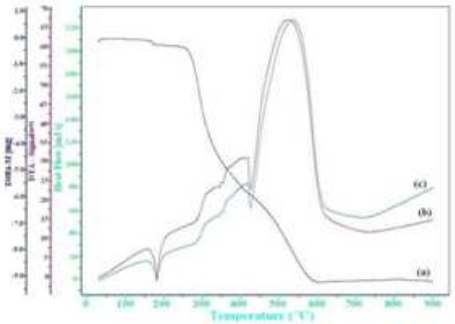

Figure 3 Thermogram of n- butyl THPM (a) TGA (b) DTA (c) DSC

## Conclusions:

The nano particles of n-butyl THPM and PPHP were synthesized by micro-emulsion technique. Crystalline structure was evaluated by powder XRD studies and the average size of crystallites was obtained by using Scherrer's formula. The FTIR spectra ruled out the presence of oil phase or surfactants in the sample. The thermal stability of the nano particles was slightly higher than those of the bulk. The FTIR and TGA studies were repeated after six months and indicated no change in the results suggesting good stability of samples under atmospheric conditions.

## Acknowledgements:

The author is thankful to Dr. Poorvesh M. Vyas for the inputs and Prof. H.H. Joshi for his keen interest.

## References:

1. Keck C.M.,Kobierski S.,Mauludin R.,Muller R.H., Second generation of drug nano-crystals for delivery of poorly soluble drugs, Smartcrystal technology, Dosis,2008,2(24):124-28.
2. J.Lee, Drug nano and micro-particles processed into solid dosage forms: Physical properties, J Pharm. Sci., 2003, 92(10), 2057-2068.
3. Bellare J., Nanotechnology in modern, traditional and alternative medicines, Preceedings, The ICMR Strategic Thrust Symposium, Mumbai, India , 2012.
4. Kayser O., Lemke A., and Hernandez – Trejo N., The impact of nanobiotechnology on the development of new drug delivery systems, Curr. Pharma. Biotechnol. 2005, 6,3-5.
5. Löffler M. and Zameitat E., Pyrimidine biosynthesis, Encyc. Biol.Chem., 2004, 3, 600-605.
6. Eicher T. and Hauptmann S., The Chemistry of Heterocycles: Structure, Reactions, Syntheses, andApplications, 2ndEdition, Wiley –VCH. Weinheim, Germany, 2003.
7. Pal B. K. and Moulik S. P., Uses and applications of micro-emulsions, Curr. Sci., 2001, 80, 990-1001.
8. Vyas P. M., Pansuriya A. M., Naliapara Y. T. and Joshi M.J., Synthesis and Characterization of n-Butyl 4-(3,4-Dimethoxyphenyl)-6-Methyl-2-Thioxo-1,2,3,4Tetrahydropyrimidine-5-Carboxylate Nanocrystalline Particles by Water/Oil Micro-emulsion Method, Int. J. Nanosci., 2011, 10, 1237-1244.
9. Vyas P.M., Ph.D. Thesis, Saurashtra University, Rajkot , 2012.

*****