PHYSICOCHEMICAL AND *IN VITRO* PHARMACOKINETIC COMPARISION OF TRADITIONAL NANOMILLED AND NOVEL NANOACTIVE™ DRUG FORMULATIONS

NanGenex
Member of the DRGT Group

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Introduction

Most compounds that enter drug development are lipophilic and exhibit unfavorable solubility and dissolution characteristics. Nanoformulation is one of the most progressive fields in pharmaceutical industry to increase solubility, bioavailability as well as reduce food effect of such active ingredients. Nanomilling is a popular top-down method used to create submicron-sized particles from drug crystals. However, this is a tedious, time and energy consuming process.

NanGenex has developed the NanoActive™ technology utilizing controlled precipitation of the drug in a continuous flow instrument [1]. This process runs at ambient temperature and pressure, therefore, it requires considerably less energy, while controlling process parameters is an easy task to accomplish. The process yields polymeric nanoparticles with increased solubility/dissolution characteristics.

Experimental methods

- NanoActive™ technology was used to prepare novel nanosized drug formulations, while nanomilled samples were prepared by a Planetary Mono Mill Pulverisette 6 (Fritsch) milling apparatus. Solid formulations were prepared by spray-drying and freeze-drying. The solid forms were redispersed in water or in biorelevant media and the resulting colloid systems were characterized
- The particle size and size distribution was characterized using DLS
- Apparent solubility and permeability of the redispersed systems were measured by filtration and sink PAMPA
- Crystal structure of the different preparations was investigated by powder XRD diffractometer and by Raman spectroscopy

Results and Discussion

Nanosized supramolecular complexes of Telmisartan [2], Candesartan cilexetil [3], Olmesartan medoxomil [4] and Aprepitant [5] were prepared as published earlier. Nanomilled formulations of the same compounds were prepared with the same composition used in the NanoActive™ formulations.

Particle size analysis showed that nanomilled samples had larger particle size and often showed polydispersed size distribution, while NanoActive™ formulations were smaller in size and showed monodisperse size distribution.

Compounds formulated using the continuous flow precipitation technique exhibited superior dissolution; apparent solubility values were up to 20 times higher when compared to nanomilled samples.

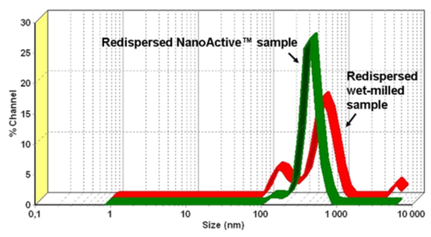
Structural analysis showed that reference and nanomilled samples were crystalline, while NanoActive™ formulations were amorphous/like.

Comparative examples showed that controlled precipitation in a continuous flow instrument yields novel structures with improved *in vitro* pharmacokinetic properties. PAMPA permeability was also up to 6 times higher for the NanoActive™ formulations.

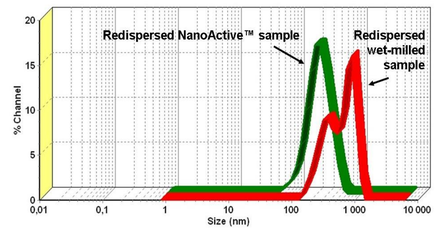
Particle size and size distribution

Comparison of the particle size and size distribution of the nanoformulae having the same composition

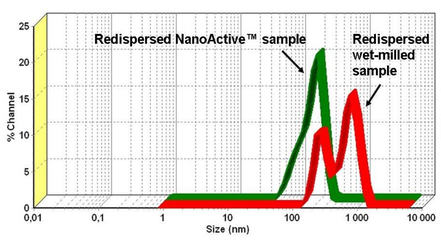
Telmisartan



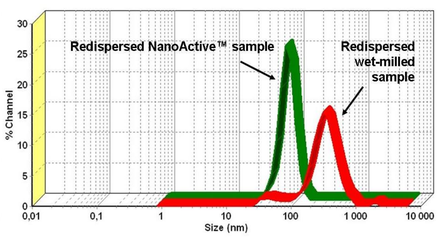
Candesartan Cilexetil



Olmesartan medoxomil

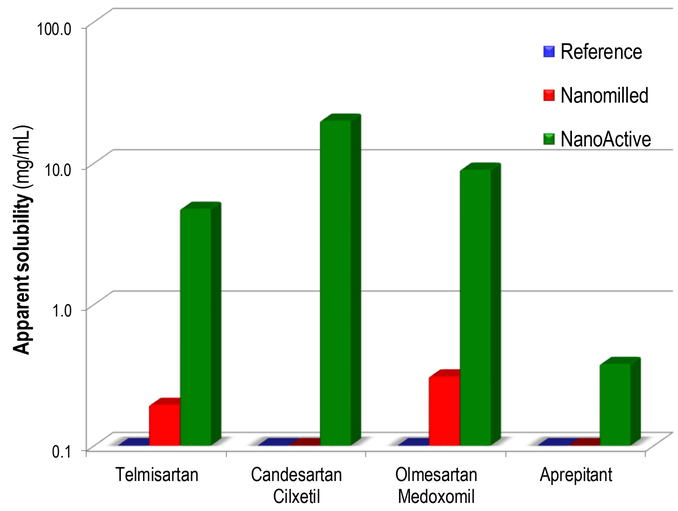


Aprepitant



Apparent* solubility enhancement

Comparison of the solubility of the nanoformulae having the same composition



* Determined by filtration through a 20nm filter

Solubility and redispersibility in time

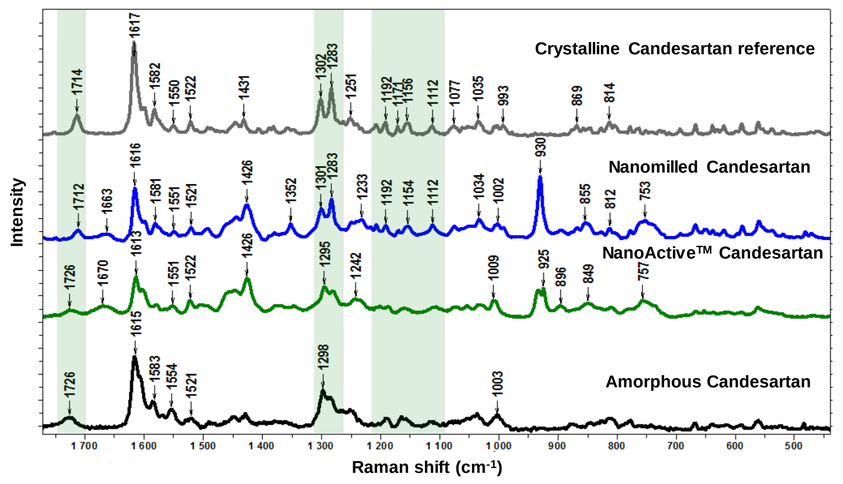
		Particle size d_{90} (nm)*		Apparent solubility (mg/mL)	
		Right after the production	After 3 months	Right after the production	After 3 months
Telmisartan	Nanomilled	1000 *polydisperse*	1024 *polydisperse*	0.195	0.218
	NanoActive™	255	242	4.120	3.820
Candesartan cilexetil	Nanomilled	828 *polydisperse*	701 *polydisperse*	0.259	0.140
	NanoActive™	350	571	>20	>20
Olmesartan medoxomil	Nanomilled	1250 *polydisperse*	1356 *polydisperse*	0.310	0.610
	NanoActive™	342	408	6.990	7.010
Aprepitant	Nanomilled	652 *polydisperse*	745 *polydisperse*	Not detectable	Not detectable
	NanoActive™	105	107	0.380	0.370

* 90% of particles are less than this size

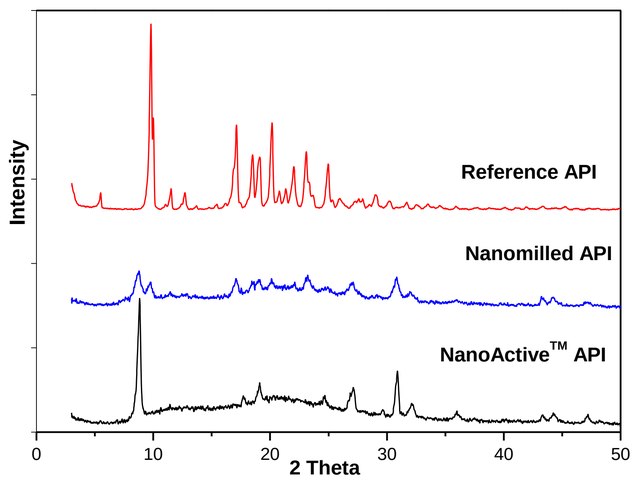
Structural comparison of nanoformulae measured by XRD and Raman microscopy

Candesartan Cilexetil

Raman spectra

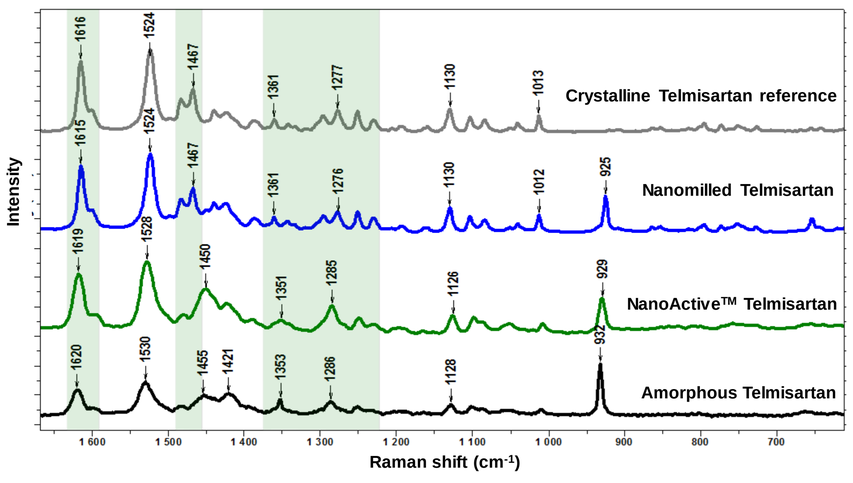


X-ray diffractogram

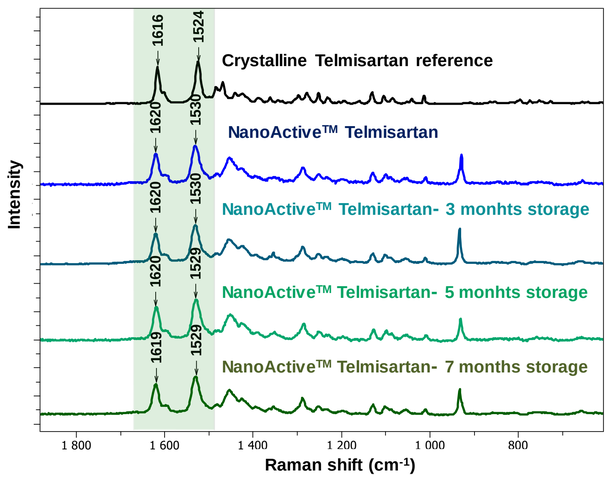


Telmisartan

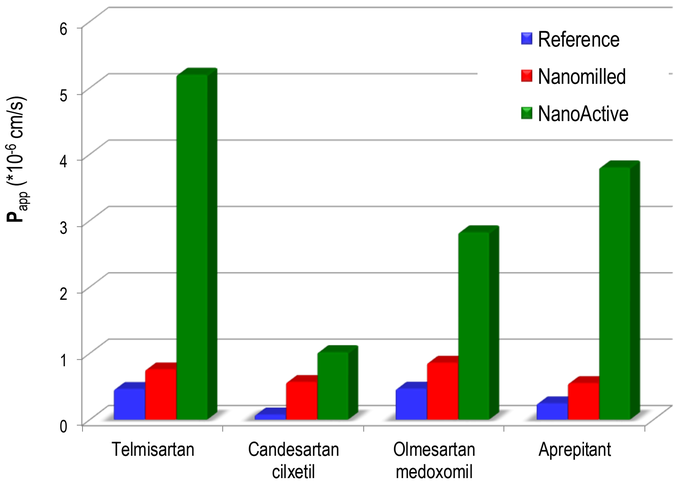
Raman spectra



Structural stability of NanoActive Telmisartan

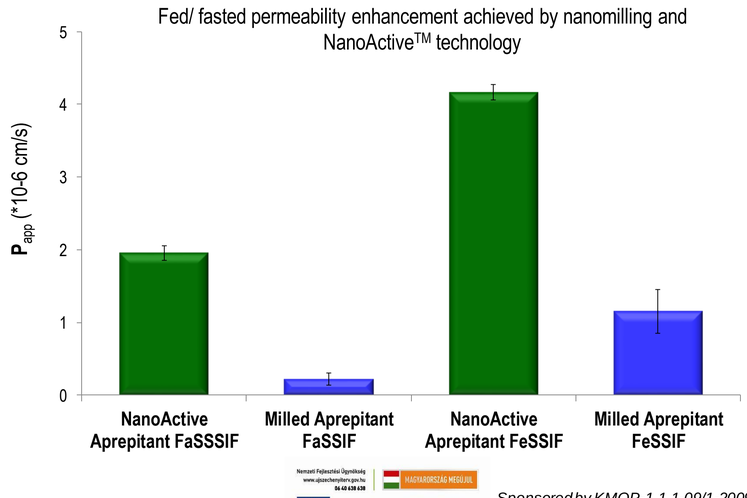


Permeability enhancement achieved by nanomilling and NanoActive™ technology



Aprepitant

Fed/ fasted permeability enhancement achieved by nanomilling and NanoActive™ technology



Sponsored by KMOP-1.1.1-09/1-2009-0025

References

1. Instrument and process for nanoparticles production in continuous flow mode, WO2009/133418
2. Nanostructured Telmisartan compositions, process for the preparation thereof and pharmaceutical compositions containing them WO/2010/146406
3. Nanoparticulate Candesartan Cilexetil compositions, process for the preparation thereof and pharmaceutical compositions containing them, WO/2010/146409
4. Nanoparticulate Olmesartan Medoxomil compositions, process for the preparation thereof and pharmaceutical compositions containing them, WO/2010/146408
5. Nanostructured Aprepitant compositions, process for the preparation thereof and pharmaceutical compositions containing them, WO/2011/158053