Research Article

International Journal of Pharmaceutical Biological and Chemical Sciences

e-ISSN: 2278-5191

STABILIZED ACECLOFENAC NANOSUSPENSION: DEVELOPMENT AND IN VITRO CHARACTERIZATION

Satyanarayan Pattnaik

Talla Padmavathi College of Pharmacy, Kareemabad, Warangal, Telangana, India

***Corresponding Author Email: saty3000@yahoo.com**

ABSTRACT:

Poor solubility of drug candidates imposes challenge during drug development process. Improvement of dissolution of BCS II drugs will improve its bioavailability upon oral administration. In this study, aceclofenac (a BCS II drug) nanosuspensions were prepared using a very simple top down approach and various concentrations of surfactant were used to optimize the nanosuspension. Surfactant concentration at a level of 0.5% was found to improve the dissolution rate of aceclofenac due to significant decrease in particle size in the nanosuspension.

KEYWORDS:

Aceclofenac, BCS II, Poor solubility drug, Nanosuspension.

INTRODUCTION

Formulations of drugs with poor aqueous solubility are problematic with respect to their biopharmaceutic quality, since slow and erratic dissolution prevent the rapid and complete absorption of these compounds from the gastrointestinal tract. These problems have been handled by adopting various approaches [1-3]. The main advantage of nanosuspension method is the increase of saturation solubility and consequently the increase in the dissolution rate of the drug. Liversidge et al. has developed NanoCrystals® by pearl milling drug powder suspension for hours up to several days [4]. In vivo studies revealed improved bioavailability, enhanced absorption rate, improved dose proportionally, reduced fed/fasted variability and reduced inter-subject variability [5, 6]. Müller et al. further developed drug nanosuspensions (DissoCubes®) by high pressure homogenization in the presence of a suitable surfactant [8]. Those formulations were prepared by passing of a microparticle drug suspension under high pressure through a small homogenization gap. High pressure homogenization is also a technique for the preparation of solid lipid nanoparticles (SLN™). In vivo studies of spironolactone SLN in rats induced a 5.7-fold increase in AUC and a similar improvement based on Cmax [9].

Mutalik et al [10], in an attempt to improve dissolution rate (and hence bioavailability) of aceclofenac, demonstrated the feasibility of co-crystals with chitosan. Surface solid dispersion of aceclofenac/microcrystalline cellulose also found to improve the dissolution rate of acelofenac.[11] In the present study, aceclofenac nanosuspensions were developed to improve the poor dissolution of the drug.

METHODS

Preparation of aceclofenac nanosuspension

Aceclofenac nanosuspensions were prepared as per the formula given in **Table 1**. First Vitamin E TPGS (D-alpha tocopheryl polyethylene glycol 1000 succinate) was dissolved in demineralized water to form an aqueous surfactant solution. The dissolution process was performed under magnetic stirring at 500 rpm. The solution was heated at 50 °C to achieve a faster dissolution of the product and cooled down at room temperature before use. Sodium CMC was then added while stirring to the above mentioned solution of surfactant. Finally aceclofenac was added and mixed for

one hour. The suspension obtained was then coarsely dispersed with a homogeniser at 5000 rpm for 15 mins. The resultant nanosuspension formulations were stored in screw capped vials in desiccators.

Particle size analysis

The size of drug nanoparticles was measured by dynamic laser light scattering (Nanoparticle size analyzer, Microtrac flex). Before analysis, the drug suspension was diluted by purified water to 0.2 mg/ml. Poly dispersion index (PDI), Graphic mean size (Mz) & calculated surface area (Cs) were used to interpret the results of particle size analysis.

In vitro dissolution studies

The *in vitro* dissolution studies were carried out using USP Type II dissolution apparatus. The dissolution media used was 900 ml of 1% sodium lauryl sulfate (SLS) solution in distilled water. The dissolution studies were carried out for 60 minutes. The dissolution medium was kept in thermostatically controlled water bath, maintained at 37±0.05 °C. Basket rotation was adjusted to 100 rpm. At definite intervals, 5 ml samples were withdrawn and analyzed spectrophotometrically at 274 nm for the drug release. At each time of withdrawal, 5 ml of fresh corresponding medium was replaced into the dissolution flask to maintain the sink condition.

RESULTS AND DISCUSSIONS

Particle size analysis

The particle size analysis for the raw aceclofenac and fabricated nanoparticles were performed and the data are presented in **Table 2**. Poly dispersion index (PDI), Graphic mean (Mz) & calculated surface area (Cs) were used to interpret the results of particle size analysis (**Table 2**). Graphic Mean provides a less coarse-particle weighted mean particle size than mean diameter of the volume distribution. While it includes the median value, it can provide a different and possibly better control value since both small particles and large particles are included in the calculation. Smaller graphic mean (Mz) values indicating smaller particles were found when the concentration of surfactant stabilizer i.e. Vitamin E TPGS was increased from 0% to 1%. The Mz value for the raw aceclofenac was found maximum (213.8 nm) indicating bigger particles. The concentration of surfactant stabilizer found to influence the particle size. Stabilizers help in preventing growth and stabilize the particles essentially by adsorption at the solid–liquid interface and reduction of the interfacial tension leading to an increased rate of nucleation [12].

Poly dispersion index (PDI) indicates the width of particle size distribution curve. Smaller PDI indicate narrow particle size distribution which is quite often desired for synthesis of drug nanoparticles. In the present investigation, for the nanosuspensions, the PDI values found less than 0.5 (**Table 2**). Raw drug resulted in broader particle size distribution (PDI values greater than 1).

Calculated surface area (Cs) is an indication of specific surface area. The Cs values were found to increase when stabilizers are used (**Table 2**).

In vitro dissolution Studies

In vitro dissolution studies of raw aceclofenac, prepared nanosuspensions were carried out in distilled water containing 1% sodium lauryl sulfate (SLS). The surface tension is lowered by addition of SLS in an attempt to mimic *in vivo* conditions [13, 3].

The studies revealed improved dissolution of aceclofenac through the process of nanonization carried out in presence of stabilizer surfactant (**Fig 1and Table 2**). Among the concentrations of surfactant stabilizer studied in this investigation, 0.5% was found most efficient which lead to highest dissolution (AN3; 91.21 ± 3.016%). Increased concentration of stabilizers reduced particle size and hence improved effective surface area for dissolution.

Table 1: Formulation of aceclofenac nanosuspension

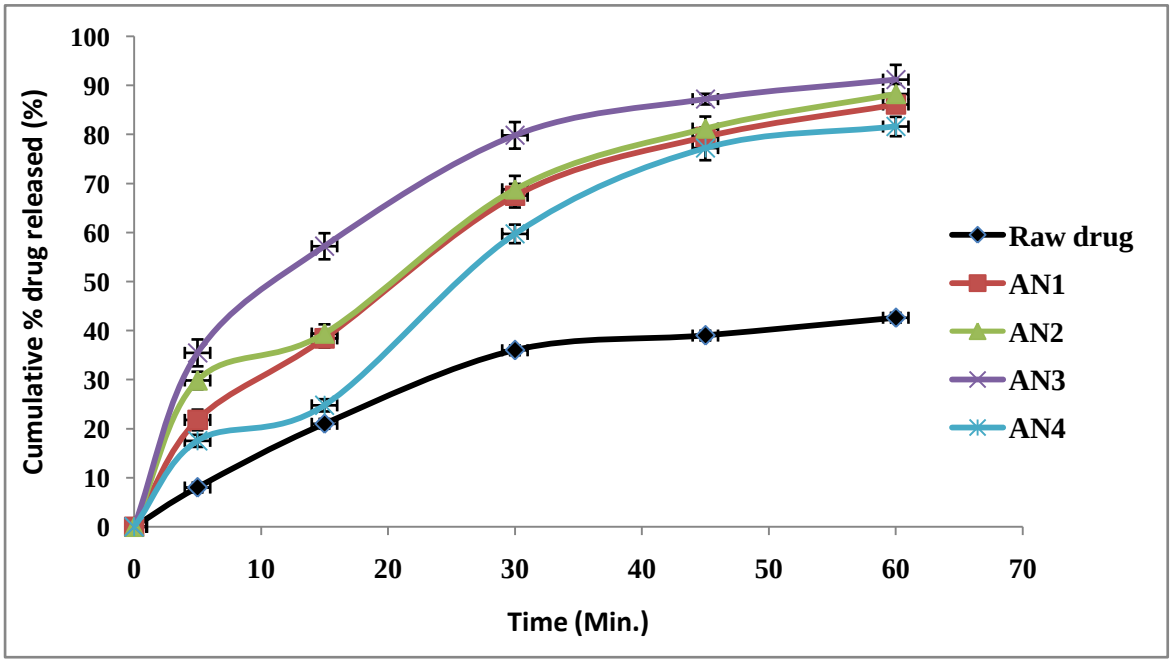
Formulation codes	Aceclofenac (%)	Sodium CMC (%)	Vitamin E TPGS (%)	Demineralized Water (%)
AN1	10	0.5	0	89.5
AN2	10	0.5	0.1	89.4
AN3	10	0.5	0.5	89
AN4	10	0.5	1	88.5

Table 2: Dissolution and particle size analysis of nanosuspensions

Product code	Cumulative % drug dissolved at 1 hr*	Particle size analysis		
		Polydispersion index (PDI)	Graphic mean size (Mz, nm)	Calculated surface area (Cs, M^2/cc)
Raw drug	42.63±2.131	1.3811	213.8	57.82
AN1	86.14± 1.226	0.2517	79.2	68.23
AN2	88.27± 2.053	0.2581	78.5	70.51
AN3	91.21 ± 3.012	0.2234	76.2	71.23
AN4	81.64± 1.973	0.2243	92.3	62.43

* Data presented as mean± standard deviation.

Figure 1: Dissolution profile of raw drug and nanosuspensions. Error bars indicate standard deviation



CONCLUSION

In this study, aceclofenac nanosuspensions were prepared using a very simple top down approach and various concentrations of surfactant were used to optimize the nanosuspension. Surfactant concentration at a level of 0.5% was found to improve the dissolution rate of aceclofenac due to significant decrease in particle size in the nanosuspension. Further preclinical investigations have to be performed to assess the bioavailability of the nanosuspension.

Conflicts of interest: The authors disclose no conflicts of interest.

REFERENCES

1. Satyanarayan Pattnaik, Kalpana Swain, Jupally Venkateshwar Rao, Sanjeev Kumar Subudhi, Pharmaceutical nanoencapsulation strategies: a mechanistic review, Int J Pharm Biol Sci 2(1) (2012) 280-4.
2. AK Mahapatra, PN Murthy, RK Patra, S Pattnaik, Solubility Enhancement of Modafinil by Complexation with β-cyclodextrin and hydroxypropyl β-cyclodextrin: A Response Surface Modeling Approach, Drug Delivery Letters 3(2013) 210-9.
3. S Mallick, S Pattnaik, K Swain, P De, Current Perspectives of Solubilization: Potential for Improved Bioavailability, Drug Dev Ind Pharm 339(2007) 865-73.
4. G.C. Rao, M.S. Kumar, N. Mathivanan, M.E. Rao, Nanosuspensions as the most promising approach in nanoparticulate drug delivery systems, Pharmazie 59 (2004) 5–9.
5. G.G. Liversidge, K.C. Cundy, J. Bishop, D. Czekai, Surface modified drug nanoparticles United States Patent No. 5145684 (1991).
6. G.G. Liversidge, K.C. Cundy, Particle size reduction for improvement of oral bioavailability of hydrophobic drugs: I. Absolute oral bioavailabilty of nanocrystalline danazol in beagel dogs, Int. J. Pharm. 125 (1995) 91–97.
7. J. Jinno,N.Kamada, M. Miyake,K.Yamada, T.Mukai,M. Odomi, H. Toguchi, G.G. Liversidge, K. Higaki, T. Kimura, Effect of particle size reduction on dissolution and oral absorption of a poorly water-soluble drug, cilostazol, in beagle dogs, J. Control. Release 111 (2006) 56–64.
8. R.H. Müller, R. Becker, B. Kruss, K. Peters, Pharmaceutical nanosuspensions for medicament administration as systems with increased saturation solubility and rate of solution United States Patent No. 5858410 (1998).
9. P. Langguth, A. Hanafy, D. Frenzel, P. Grenier, A. Nhamias, T. Ohlig, G. Vergnault, H. Spahn-Langguth, Nanosuspension formulations for low-soluble drugs: pharmacokinetic evaluation using spironolactone as model compound, Drug Dev. Ind. Pharm. 31 (2005) 319–329.
10. S Mutalik, P Anju, K Manoj, AN Usha, Enhancement of dissolution rate and bioavailability of aceclofenac: A chitosan-based solvent change approach, Int J Pharm 350 (2008) 279–90.
11. Furqan A. Maulvi, Sonali J. Dalwadi, Vaishali T. Thakkar, Tejal G. Soni, Mukesh C. Gohel, Tejal R. Gandhi. Improvement of dissolution rate of aceclofenac by solid dispersion technique. Powder Technology.Volume 207, Issues 1–3, 15 February 2011, Pages 47–54
12. Raghavan SL, Schuessel K, Davis A, Hadgraft J. 2003. Formation and stabilisation of triclosan colloidal suspensions using supersaturated systems. *Int J Pharm*, 261, 153–8.
13. Mallick S, Pattnaik S, Swain K, De PK, Saha A, Mazumdar P, Ghoshal G. 2008. Physicochemical characterization of interaction of ibuprofen by solid-state milling with aluminum hydroxide. *Drug Dev Ind Pharm*, 34, 726–34.

***Corresponding author address**:
Email address:
saty3000@yahoo.com