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The impact of process parameters on carrier free paracetamol nanosuspension prepared using different stabilizers by antisolvent precipitation method

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ABSTRACT

Poor aqueous solubility leading to poor oral bioavailability is a bottle neck in the development of many new drug candidates; particularly the BCS class II-IV drugs. These molecules are difficult to formulate using conventional approaches and are associated with numerous formulation related performance issues. To overcome this hurdle, formulation of nanosuspension can be one promising alternative. The purpose of this study was to develop nanosuspension using paracetamol as a model drug by antisolvent precipitation method. Nanoparticles were generated by incorporating drug solution into an antisolvent, which generated rapid nucleation leading to nanosuspension. Different stabilizers including PEG, HPMC, and Pluronic F68 were used to inhibit the particle size growth of nanosuspension. The prepared nanosuspension was evaluated in terms of particle size distribution, morphology and thermal properties. Dissolution study was also performed for nanosuspension and compared with the raw powder and commercially available paracetamol suspension (Ace® suspension). Processing conditions and type of stabilizers showed marked impact on the average particle size, morphology and stability of nanosuspension batches. Although paracetamol is sparingly soluble in water, its nanosuspension formulation exhibited faster dissolution rate when compared with commercial microsuspension and raw powder.

1. Introduction

Poor water solubility and low bioavailability of drugs are great challenges for achieving optimum therapeutic outcome from different types of drug delivery systems. It is a well-known fact that more than 40% of drugs are very poorly soluble in water, which limits their absorption [1,2]. Poor water solubility leads to reduced drug absorption from the GI tract, which results in poor bioavailability [3,4]. To overcome this barrier many advance formulation methods have been approached in recent time including chemical modification, cyclodextrin method, liposomal and lipid based formulation (self-emulsifying/microemulsifying systems) [3,5–7]. Limitations of these methods, such as - change in pharmacological activity due to chemical modification as well as physical and chemical instability have led to the development of new drug formulation approach 'Nanosization'. It is the technology for converting pure drug particles (amorphous or crystalline) into nanoscales (10–1000 nm), suspended in a dispersion medium (mostly water) stabilized by polymer(s) or surfactant(s) [8]. Antisolvent precipitation is one of the attractive bottom up technique to develop nanosuspension, which is relatively simple, cost effective and can be easily scaled for industrial production of paracetamol nanosuspensions [9]. Preferably, using this technique, the drug must be dissolved firstly in an organic solvent, which is then able to mix rapidly with an antisolvent (e.g., water) [10]. High supersaturation therefore can be generated by an increased concentration gradient, which is a result of decreased diffusional pathway adjacent to the surface of drug nanoparticles. Moreover, generation of high-energy surfaces during disruption of drug crystals to nanoparticles might increase saturation solubility. As a result, it enhances dissolution velocity and improves oral bioavailability [6]. Thus with the effective nanosuspension, the decreased size of drug particles can increase the surface area to volume ratio, therefore, the rate of dissolution as well as the bioavailability will also improve. The increased surface area due to the reduction in particle size also leads to increased saturation solubility for nanosized drug particles [11].

To form stable nanosuspension, it is important to keep the particle size uniform and avoid large differences between their size for preventing different saturation solubility and concentration gradients, which will inhibit the Ostwald ripening [12]. Ostwald ripening involves small particles from the higher concentration containing higher

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saturation solubility diffuse to the area around larger particles of lower drug concentration. This forms a supersaturated solution around the large particles consequently leads to drug crystallization and growth of the large particles [13]. Among all other dosage forms of nanotechnology, formulation of nanosuspension is a promising alternative due to its cost effectiveness and simplicity in manufacturing [9,14].

Therefore, the aim of this study was to understand the impact of processing conditions, type and concentration of stabilizers (Pluronic F68, PEG 4000/6000, HPMC etc.) on average particle size, size distribution and stability of paracetamol nanosuspensions. Although paracetamol is a sparingly water-soluble drug, it was suitably used in this study as a model drug for nanosuspension formulation. Dissolution study of paracetamol nanosuspension batches was compared with raw paracetamol powder of micrometer range and marketed paracetamol suspension to evaluate the performance of nanosized drug particles.

2. Materials and methods

2.1. Materials

Paracetamol (*N*-acetyl-*p*-aminophenol) raw powder, polyethylene glycol (PEG) 4000, Pluronic F68, and Triethanolamine (TEA) were obtained from Eskayef Bangladesh Ltd. (Dhaka, Bangladesh). Paracetamol marketed product (Ace® suspension, 120 mg/5 ml) was obtained from Square Pharmaceuticals Ltd, Dhaka, Bangladesh. Polyethylene glycol (PEG) 6000, Hydroxyl propyl methyl cellulose (HPMC) and ethanol was purchased from Sigma Aldrich Co, St. Louis, MO, USA. All reagents used were of analytical grade and used without any further purification.

2.2. Methods

2.2.1. Antisolvent precipitation method

Nanosuspension was formulated by antisolvent precipitation method using water as an antisolvent. The drug was dissolved in a water miscible solvent (ethanol) and then the solution was rapidly added to the antisolvent (water) containing growth inhibitor or stabilizer. The drug solution contained paracetamol at a concentration of 60 mg/ml of ethanol.

Different stabilizers and their combinations including triethanolamine (TEA), hydroxyl propyl methyl cellulose (HPMC), PEG 6000, PEG 4000 and Pluronic F68 were investigated at different concentrations and process conditions (infusion rate, stirring rate and antisolvent temperature) to obtain a stabilized nanosuspension formulation (Table 1). Drug concentration was fixed (60 mg/ml) and selected from preliminary screening of few batches of paracetamol nanosuspension. To achieve the scalability of the process, batch size of 100 ml was produced using optimum formulation and processing conditions determined from 25 ml of small scale nanosuspension batches.

2.2.2. Inverse phase microscopy

Inverse phase microscopy (Olympus, model -AxioCamERc 5s, Japan) was initially used to characterize the particle size of the representative nanosuspension. Each sample was analyzed in triplicate.

2.2.3. Field emission scanning electron microscope (FESEM)

The surface morphology of the paracetamol nanosuspension were visualized using a Jeol JSM7600F field emission scanning electron microscope (FESEM). Samples were analyzed at a variety of magnifications (10000× and 30000×) with direct data capture of the high-resolution images onto a personal computer. The freeze-dried paracetamol nanosuspensions were scattered on double-side adhesive carbon tapes, which were attached to FESEM specimen mounts. The specimens were sputter-coated for 2 min to obtain uniform coating on the sample by Jeol JFC-1600 Auto fine coater.

2.2.4. Particle size distribution and determination of zeta potential

The average particle size and zeta potential values of the nanosuspension batches were measured using a Malvern Zetasizer Nano ZS90 (Malvern Instruments) which were carried out at 25 °C using plain folded capillary zeta cells. The diluted samples were placed directly into the cuvette and the data were collected for 10 times. All experiments were performed in triplicates and the average value was used from the each set of data.

2.2.5. Polydispersity index (PDI)

PDI values were measured to understand the size distribution of the nanoparticles and the value range between 0.000 and 1.000, which demonstrates narrow to very wide size distribution of the particles. The equation related to PDI is, D (0.9)/D (0.1)/D (0.5) where, D (0.9), D (0.5) and D (0.1) represents particle size immediately above 90%, 50% and 10% of the sample respectively [15].

2.2.6. Differential Scanning Calorimetry (DSC)

The thermal behavior of the pure paracetamol raw powder, PEG 4000 and freeze-dried paracetamol nanosuspension (paracetamol with PEG 4000) was characterized using Differential Scanning Calorimetry (DSC), by DSC Q200 (TA Instruments, USA). The samples were heated at a rate of 10 °C/min from 25 to 300 °C under dry nitrogen at a flow rate of 25 mL/min. A standard aluminium sample pans were used. About 3–5 mg samples were hermitically sealed for analysis. The DSC temperature and enthalpic scale were calibrated using indium standard.

Table 1
Different batches of paracetamol nanosuspension formulation with average particle size and PDI value (± SD where n = 3).

Batch No	Stabilizer	Amount of Stabilizer (mg/ml water)	Infusion rate (ml/sec)	Antisolvent Temperature (°c)	Agitation Rate (rpm)	Average particle size (nm)	PDI	Zeta Potential (± mV)
01	Pluronic F68	1.67	0.25	45 ± 2°c	1200	179.0 ± 2.1	0.37 ± 0.01	−18.2 ± 3.3
02	Pluronic F68	3.33	0.25	45 ± 2°c	1200	311.0 ± 3.0	0.40 ± 0.03	−24.4 ± 1.8
03	PEG 6000	1.67	0.125	23 ± 2°c	1200	348.0 ± 7.0	0.29 ± 0.04	N/A
04	PEG 6000	3.33	0.25	23 ± 2°c	1200	530.0 ± 29.5	0.40 ± 0.06	23.8 ± 2.2
05	PEG 4000	1.67	0.25	45 ± 2°c	1200	344.0 ± 12.4	0.32 ± 0.01	−8.5 ± 1.1
06	PEG 4000	3.33	0.25	45 ± 2°c	1200	374.0 ± 5.6	0.67 ± 0.08	N/A
07	PEG 6000	1.67	0.25	45 ± 2°c	1200	222.0 ± 4.8	0.36 ± 0.03	−11.6 ± 0.9
08	PEG 4000	1.67	0.25	23 ± 2°c	1200	242.0 ± 6.1	0.42 ± 0.01	N/A
09	HPMC	1.67	0.25	45 ± 2°c	1200	479.0 ± 30.0	0.84 ± 0.05	−4.2 ± 0.8
10	Pluronic F68	1.67	0.125	45 ± 2°c	1200	273.0 ± 12.5	0.54 ± 0.02	−11.4 ± 1.0
11	Pluronic F68 + TEA	1.67 + 1.67	0.25	45 ± 2°c	1200	183.0 ± 5.3	0.39 ± 0.01	−7.6 ± 0.8
12	PEG 6000 + TEA	1.67 + 1.67	0.25	45 ± 2°c	1200	416.0 ± 25.1	0.53 ± 0.03	−29.8 ± 2.4
13	Pluronic F68	1.67	0.25	45 ± 2°c	600	370.0 ± 16.2	0.70 ± 0.06	N/A
14	PEG 4000	1.67	0.25	45 ± 2°c	600	402.0 ± 27.6	0.63 ± 0.02	N/A