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Research Article

FORMULATION OF DEXIBUPROFEN SOLID LIPID NANO PARTICLES AND ITS EVALUATION BY *IN VITRO* DISSOLUTION STUDY

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ABSTRACT
Dexibuprofen is a poorly water soluble nonsteroidal anti-inflammatory drug, prescribed for moderate to severe pain and inflammation. It is the active dextrorotatory enantiomer of ibuprofen and has better anti-inflammatory effect. Hence present study was carried out to enhance dissolution properties of dexibuprofen through the preparation of solid lipid nano particles (SLNPs) using stearic acid as lipid, lutrol F-68 (Poloxamer) as surfactant and tween-80 as stabilizer by hot homogenization method. Six formulations were prepared in different ratios and were designated as DNP1 to DNP6. USP type II rotating paddle dissolution studies in 900 ml distilled water at 50 rpm to a temperature of 37°C ± 0.5°C were performed for evaluation of solid lipid nano particles. UV spectrophotometric method was selected for assay as well as *in-vitro* dissolution studies at λ_{max} 222 nm. The drug release profile followed zero order and first order kinetics. *In-vitro* studies showed that solubility and dissolution rate of dexibuprofen were significantly improved by SLN formulation than the drug alone. This result may trigger more research in the intension of exploiting this feature to develop a novel drug delivery system for dexibuprofen with enhanced bioavailability.
Keywords: Dexibuprofen, solid lipid nano particles, hot homogenization method, dissolution study.

INTRODUCTION

Dexibuprofen [S (+)-ibuprofen] is considered as pharmacologically active enantiomer of racemic ibuprofen. It is a nonsteroidal anti-inflammatory drug with analgesic action which acts by inhibiting prostaglandin synthesis and used for the management of pain and inflammation associated with osteoarthritis including dysmenorrhea and dental pain with dose range 200-400 mg 2-3 divided doses, as conventional tablets. Due its short biological half-life 1.8-3.5 hours, it requires multiple dosing. It leads to fluctuation in the drug blood levels and dose related adverse effects, multiple dosing also fail to release the drug at the desired rate and in the desired amount which often results in poor patient compliance and inefficient therapy[1]. It has less gastric damage belongs to class II of Biopharmaceutical Classification System (BCS) having low water solubility which is rate limiting step in absorption of drug in GI tract[2,3]. Oral ingestion is the most convenient and commonly employed route of drug delivery due to its ease of administration, high patient compliance, cost effectiveness, least sterility constraints and flexibility in the design of dosage form. As a result many of the generic drug companies are inclined more to produce bioequivalent oral drug product. However, the major challenge in the design of oral dosage form lies with their poor bioavailability. The oral bioavailability depends on several factors including aqueous solubility, drug permeability, dissolution rate, first-pass metabolism, pre-systemic metabolism, and susceptibility to efflux mechanisms. The most frequent causes of low oral bioavailability are attributed to poor solubility and low permeability[4-7]. Solid lipid nanoparticles (SLNs) are considered to be the most effective lipid based colloidal carriers, introduced in early nineties. This is one of the most popular approaches to improve the oral bioavailability of the poorly water soluble drugs. SLNs are in the submicron size range of 50-1000 nm and are composed of physiologically tolerated lipid components which are in solid state at room temperature. Due to biodegradable and bio acceptable nature of SLN these are less toxic than polymeric nanoparticles and it also overcome some disadvantages of traditional colloidal drug carrier system. Development of SLNs is one of the emerging fields of lipid nanotechnology with several potential applications in drug delivery, clinical medicine and research, as well as in other discipline. Due to their unique size-depended properties, lipid nanoparticles offer the possibility to develop new therapeutics. The ability to incorporate drugs into nanocarriers offers a new prototype in drug delivery that could hold great promise for attaining the bioavailability enhancement along with controlled and site specific drug delivery[8-10]. In the present investigation, dexibuprofen was selected as a model drug for dissolution enhancement studies. The objective of this research was to improve solubility, dissolution and bioavailability of dexibuprofen by forming solid lipid nano particles with stearic acid as solid lipid.

MATERIALS AND METHODS

Materials

Dexibuprofen was a gift sample from Beximco Pharmaceuticals Ltd, Dhaka, Bangladesh. Stearic acid was procured from Balami Fine Chemicals, India. Tween-80, lutrol F-68 (Poloxamer) were received from BASF, Germany. All other reagents and solvent used were of analytical grade.

Preparation of dexibuprofen SLNPs by hot homogenization method

Solid lipid nano particles of dexibuprofen were prepared using the lipid (stearic acid); surfactant (lutrol F-68) and stabilizer (tween-80) at different proportion by hot homogenization technique using the high speed homogenizer[7,11-14]. This method is carried out at temperatures above the melting point of the lipid and therefore regarded as

the homogenization of emulsion. The organic phase was prepared by dissolving the drug and surfactant in acetone and mixing it with the melted stearic acid, which was further, poured into aqueous tween-80 solution (maintained at the same temperature as that of organic phase) of various concentrations which acts as a stabilizer and emulsified by a homogenizer at 12000 rpm for 2 hours. The formulation was then removed from water bath and the dispersion of SLNs was mixed gently by slow magnetic stirring (1 hour) at room temperature until cooling. In general, higher temperatures result in lower particle sizes due to the decreased viscosity of the inner phase and high kinetic energy of the particles (Table 1).

***In vitro* dissolution studies of dexibuprofen SLNPs**

In vitro dissolution studies of the pure drug and dexibuprofen SLNs were carried out to estimate the cumulative% of drug release with respect to time. Distilled water (900 ml) was placed in each vessel of the USP type II rotating paddle dissolution apparatus (Veego Vda6 DR, Germany). Two SLNs granules were placed in each vessel and the medium was allowed to equilibrate at 50 rpm to a temperature of 37°C ± 0.5°C for 50 minutes. 5 ml of the sample was withdrawn at definite time interval (10, 20, 30, 40 and 50 minutes) consecutively and replaced by fresh media to maintain the sink condition. The absorbances of sample were measured spectrophotometrically at λ_{max} 222 nm on a UV-Visible spectrophotometer (UVmini-1240, Shimadzu, Kyoto, Japan) and the values of dissolution efficiency were calculated. It was made clear that none of the ingredients used in the formulations interfered with the assay[15].

Release Kinetic modeling

There are a number of kinetic models, which described the overall release of drug from the dosage forms. Because qualitative and quantitative changes in a formulation may alter the drug release and *in vivo* performance, developing tools that facilitate product development by reducing the necessity of bio-studies is always desirable. In this regard, the use of *in vitro* drug dissolution data to prdict *in vivo* bio-performance can be considered as the rational development of controlled release formulations[16].

Zero order release

In zero order kinetics the release rate is independent of the concentration of drug at GIT; i.e. whatever the amount of drug at GIT or absorption site release rate remains constant throughout the period of release.

$$Ct = C_0 + K_0 t$$

Where, Ct is the amount of drug dissolved in time t, C_0 is the initial amount of drug in the solution (most times, $C_0 = 0$), K_0 is the zero-order release rate constant expressed in units of concentration / time and t is the time in hours

To study the release kinetics, data obtained from *in vitro* drug release studies were plotted as cumulative % of drug released *versus* time[17].

First order release

Most currently marketed sustained release formulations, however, do not release drug at a constant rate. In many instances, the rate of appearance of drug at the absorption site can be approximated by an exponential or first order process in which the rate of drug release is a function only of the amount of drug remaining in the dosage form[18].

$$\mathbf{Log\ C = Log\ C_0 - \frac{kt}{2.303}}$$

Where, C is the concentration of drug at time t, C_0 is the initial concentration of drug, K is the first order release rate constant expressed in units of time-[1].

The data obtained are plotted as log cumulative % of drug remaining *versus* time.

RESULTS

In-vitro drug release study of dexibuprofen from various SLN formulations was done by USP type-Π apparatus. The *in vitro* dissolution data of all the formulations were satisfied by different kinetic models. The zero order rates describe the systems where the drug release is independed of its concentrations. Figure 1 and 2 shows the cumulative amount of drug release vs time for zero order kinetics. The first order which describes the systems where release rate is concentration dependent is illustrated by Figure 3 and 4, which shows the log cumulative percent of drug remaining vs time. Cumulative % of drug release (Figure 5) for different formulations (DNP1 to DNP6) shows that the release rate is much higher from the SLN formulations than the pure drug. The reason for the poor dissolution of pure drug could be poor wettability and agglomeration of particles. DNP3 with the stabilizer concentration 2 % gives 50.74 % drug release that is higher dissolution rate than other formulations in 50 minute period of time. Hence 2 % stabilizer concentration is considered as optimum for this type of formulations. Further, in case of DNP6 with same stabilizer ratio but reduced surfactant concentration, no marked increase in dissolution was observed.

Table 1: Formulation of dexibuprofen SLNPs through hot homogenization method

Formulation code with ratio	Drug (mg)	Lipid (mg)	Surfactant (mg)	Stabilizer (ml)	Acetone (ml)	Water (ml)
DNP1 (1:0.5:1:1)	1000	500	1000	1	20	20
DNP2 (1:0.5:1:1.5)	1000	500	1000	1.5	20	20
DNP3 (1:0.5:1:2)	1000	500	1000	2	20	20
DNP4 (1:1:0.5:1)	1000	1000	500	1	20	20
DNP5 (1:1:0.5:1.5)	1000	1000	500	1.5	20	20
DNP6 (1:1:0.5:2)	1000	1000	500	2	20	20

*DNP = Dexibuprofen nano particle

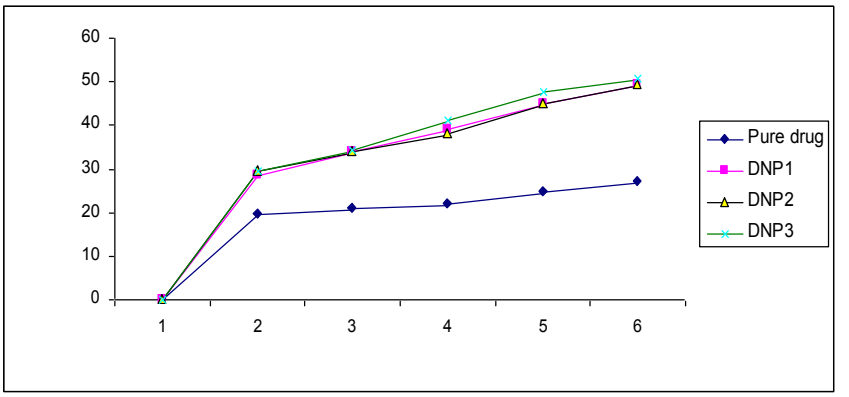

Figure 1: Zero order plot of release kinetics of dexibuprofen from different SLNPs (DNP1, DNP2 and DNP3)

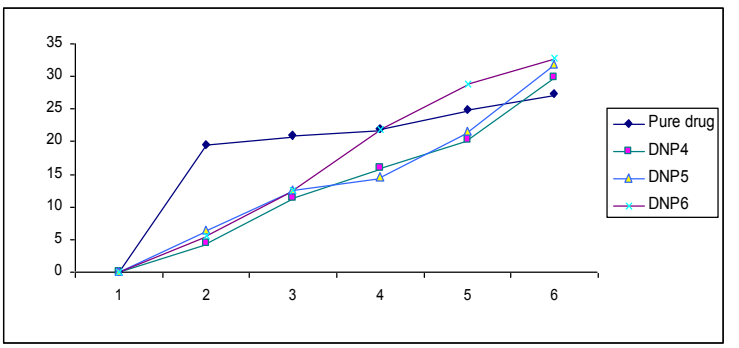

Figure 2: Zero order plot of release kinetics of dexibuprofen from different SLNPs (DNP4, DNP5 and DNP6)

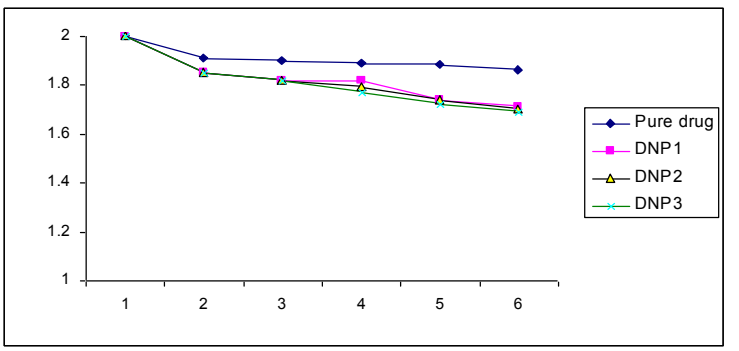

Figure 3: First order plot of release kinetics of dexibuprofen from different SLNPs (DNP1, DNP2 and DNP3)

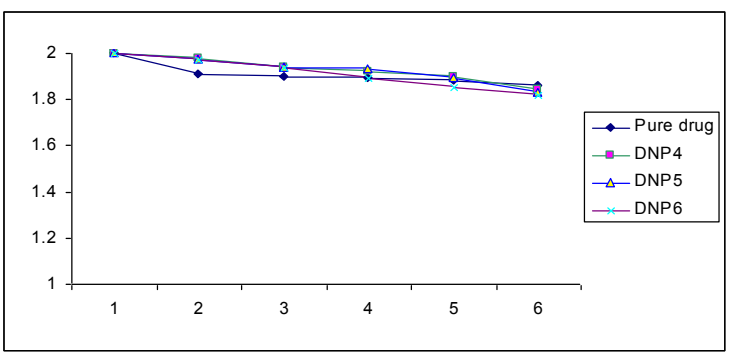

Figure 4: First order plot of release kinetics of dexibuprofen from different SLNPs (DNP4, DNP5 and DNP6)

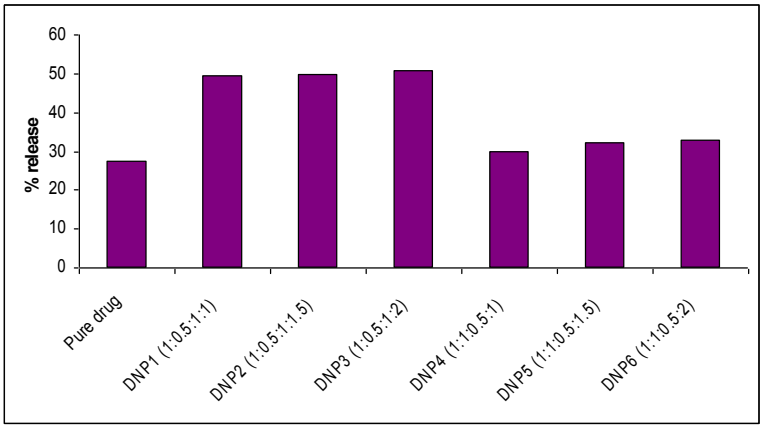

Figure 5: Graphical representations of drug release efficiency of dexibuprofen from different SLNPs as compared to pure drug (DNP1, DNP2, DNP3, DNP4, DNP5 and DNP6)

DISCUSSION

The use of solid lipid instead of liquid lipid is beneficial as it has been shown to increase control over release kinetics of encapsulated compounds and to improve the stability of incorporated chemically-sensitive lipophilic ingredients. These potentially beneficial effects are because of a number of physicochemical characteristics associated with the physical state of the lipid phase. Firstly, the mobility of reactive agents in a solid matrix is lower than in a liquid matrix and so the rate of chemical degradation reactions may be retarded. Secondly, micro phase separation of the active ingredients and carrier lipid within individual liquid particles can be controlled, thereby preventing the accumulation of active compounds at the surface of lipid particles where the chemical degradation reactions often occur. Thirdly, absorption of poorly absorbed bioactive compounds has been shown to be increased after incorporation into solid lipid nano particles. The use of solid matrix instead of liquid matrix can slow down lipid digestion thereby allowing for a more sustained release of the encapsulated compound[19]. The surfactant molecules were also necessary for emulsification as well as stabilization of SLNs. Entrapment efficiency were increased significantly by increasing both amount of surfactant and amount of lipid. This effect may be explained by increased viscosity of medium which prevents rapid diffusion of dexibuprofen into the bulk of medium increasing its entrapment efficiency[20]. With increasing surfactant concentration, it is possible that dexibuprofen gets entrapped in surfactant layer covering SLNs surface leading to higher entrapment efficiency. Higher amount of lipid also provides additional number of particles into which the drug gets entrapped. The lipid molecule also reduces the drug crystallinity followed by reduction of particle size and increases solubilization of drug as well as dissolution rate. SLNs size range bellow 300 nm is considered suitable for absorption across Peyer's patches and villi of the gastrointestinal tract[21,22]. Consequently, by considering all the above conditions it is also possible to enhance bioavailability of dexibuprofen by SLNs formation. So, the present study confirmed that dexibuprofen SLNs with lipid, surfactant and stabilizer (1:0.5:1:2) can be formulated as tablet with better dissolution characteristic.

CONCLUSION

By investigating of some effective factors, an optimized set of method variables were determined and validated for new SLN preparation. From the data shown here, it could be concluded that it is possible to produce the dexibuprofen SLNs with stearic acid, surfactant and stabilizer (1:0.5:1:2) and capable of encapsulating and enhancing bioavailability of dexibuprofen which may prove beneficial in the treatment of patients with pain and inflammation.

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