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Enhancement of dissolution rate of phenytoin by solid dispersion technology using hydrophilic polymers

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Abstract
Objective: Enhancement of dissolution rate of Phenytoin by solid dispersion technology using hydrophilic polymers and solid state characterization & dissolution behavior
Methods: Formulation parameters evaluated by the solvent evaporation method at drug: different polymer ratios
Results: The results showed that PEG 6000-based solid dispersion exhibited significantly higher phenytoin dissolution. Phenytoin has high melting point, which is indicative of strong crystal lattice energy. All solid dispersions of phenytoin prepared with PEG 6000 and poloxamer 407 polymers showed enhanced drug solubility over the pure phenytoin (0.11) mg/ml in distilled water and (0.23)mg/ml in phosphate buffer 6.8. The *in vitro* release studies were carried out for the phenytoin solid dispersions prepared by melting method. The dissolution rate of pure phonation was very poor and during 120 min a maximum about 28.55% of the drug was released.
Conclusion: The formulation of solid dispersion of a drug with hydrophilic crriers is a potential approach used to improve the solubility and dissolution rate of practically water insoluble or less soluble drugs

Keywords: phenytoin, PEG 6000, poloxamer 407, enhanced drug solubility, dissolution rate

Introduction

Development of bioavailable dosage form of these drugs is the most important challenge faced by the formulators. The oral route of administration is the most convenient and preferred method of drug delivery. At least 90% of all drugs used to produce systemic effects are administered by oral route When a drug is taken orally it passes through the mouth, esophagus, stomach, duodenum, jejunum (small intestine), colon (large intestine) and finally leaves the body if not absorbed [1]. Oral bioavailability of drugs can be improved by the enhancing solubility and dissolution rate of poorly water soluble drugs, and another is enhancing the permeability of poor permeable drugs [2]. The formulation of poorly soluble compounds for oral delivery at present is one of the most frequent and greatest challenges to formulation scientists in the pharmaceutical industry [3]. Oral absorption of poorly water-soluble drugs.Solid Dispersion is defined as a dispersion of one or Solid dispersion technique was firstly demonstrated by Sekiguchi and Obi in 1961, to increase the dissolution and more active ingredients in an inert carrier, usually highly water-soluble compound, which could be prepared by different methods including melting, solvent and melting-solvent techniques [4, 5, 6, 7].

To examine the role of specific drug-polymer interactions during dissolution on drug solubility and bioavailability, the polymers were formulated with the anticonvulsant drug phenytoin, which is a poorly water-soluble BCS class II drug where oral absorption is limited by the drug solubility. Solid dispersions (SD) were prepared via Melt of phenytoin with the polymer excipient models to contain 10% and 25% by weight drug loading [8].

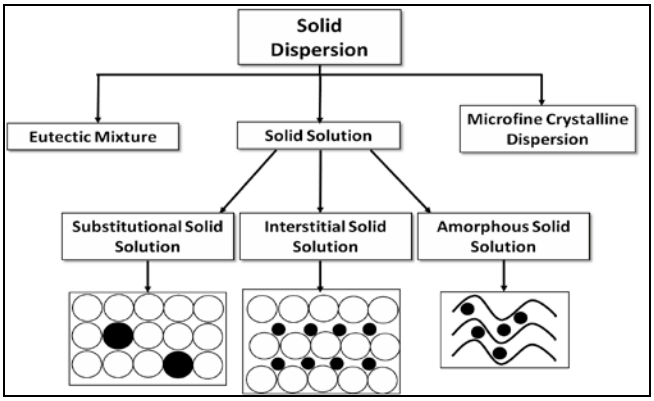

Fig 1: Classification of Solid dispersion

Materials and Method

Phenytoin was obtained from Precise Chemipharma Pvt. Ltd. PEG 6000 Rajesh Chemicals, Mumbai. Polaxamer 407 Ozone ®international. Mumbai. All other chemicals and ingredients were used for study are of Analytical grade.

Method

Preparation of solid dispersion by melting method [9-14]

The melting or fusion method was used to prepare PEG 6000 and Poloxamer 407based solid dispersion of Phenytoin in the ratio of 1:1,1:2 and 1:3 heated directly until it melted. The melted mixture is then solidified rapidly in an ice-bath under constant stirring. The solid mass of PEG 6000 and Poloxamer 407 based Phenytoin solid dispersion was finally crushed and pulverized. The obtained powder of solid dispersion was passed through sieves (No.44) and stored in desiccators until use for further studies.

Preparation of Physical Mixture [15-17]

Physical mixtures were prepared by simple mixing of two Components. The appropriate amounts of drug and carrier were blended in a mortar and pestle to form physical mixture. The mixture was passed through sieve number 44 to obtain uniform size distribution

Table 1: Composition of Phenytoin loaded solid dispersion

Formulation code	Carrier	Drug: carrier	Method
F1	PEG 6000	1:1	Melting / Fusion method
F2		1:2	
F3		1:3	
F4	Poloxamer 407	1:1	
F5		1:2	
F6		1:3	

Characterization of Solid Dispersion

a. Drug Content [18]

Drug content was determined by dissolving solid dispersions equivalent to 10mg of drug in 10ml of methanol and sonicated for 10 minutes. The volume was adjusted to 100ml with phosphate buffer 6.8. The solution was filtered through Whatman filter paper (0.22µm), suitably diluted and assayed spectrophotometrically at 232nm [19-21].

b. Saturation solubility studies [22]

The saturation solubility study of Phenytoin was done by with solid dispersion. Equivalent to 10mg drug and solid dispersion was added to screw-capped vials containing 10 ml of phosphate buffer 6.8 of PEG 6000 and Pluronic F127 with varying concentrations. Vials were shaken with magnetic stirrer for 48 hr at a controlled temperature at 37ºC±2ºC. After 48 hours the solution was filtered through Whatman filter paper (0.22µm). The filtrate was then diluted and assayed spectrophotometrically at 232nm

c. In-vitro drug release study [23, 24, 25]

The drug release was studied using USP type I apparatus at 37 ± 0.5°C and at 50 rpm using 900 ml of phosphate buffer pH 6.8 as a dissolution medium. 5ml of the sample solution Was withdrawn at predetermined time intervals, filtered, diluted suitably and analyzed spectrophotometrically at 232 nm. Equal amount of the fresh dissolution medium was replaced immediately after withdrawal of the test sample. Percentage drug dissolved at different time intervals was calculated using the Lambert-Beer's equation. The result was obtained in triplicate and the average value reported.

Fig 2: Dissolution test apparatus of in-vitro drug release

Result and Discussion

a. Drug content

The melting method is a convenient method for the preparation of solid dispersion with good drug content. Drug content of all eight batches based on PEG 6000 and Poloxamer407concentration was found to be in the range of (91.65%-95) which might be due to loss of drug during pulverization and sieving processes. It was observed that with the increase in polymer concentration drug content also increased. It indicates that the drug is uniformly dispersed in the powder formulation. Therefore, the method used in this study appears to be reproducible for preparation of solid dispersion.

Table 2: Drug content

Formulation	Drug content (%)
F1	91.73% ±0.001528
F2	93.07% ±0.001
F3	95% ±0.001528
F4	91.65% ±0.001528
F5	91.18%±0.001528
F6	92.40%±0.001

b. Saturation solubility study

All solid dispersions of Phenytoin prepared with PEG 6000 and poloxamer 407 polymers showed enhanced drug solubility over the pure Phenytoin (0.10) mg/ml in distilled water and (0.26)mg/ml in phosphate buffer 6.8. The maximum solubility achieved by using PEG 6000 especially at the ratio f3 1:3 drug-to-carriers, where the solubility was (0.88±0.001324) mg/ml. Regarding the effect of the type of poloxamer407, which was between (0.63± 0.001564) mg/ml [26]

Table 3: Saturation solubility study of solid dispersion

Formulation code	Saturation solubility in mg/ml
Pure drug in PBS 6.8	0.33
F1	0.423
F2	0.632
F3	0.787
F4	0.344
F5	0.422
F6	0.603

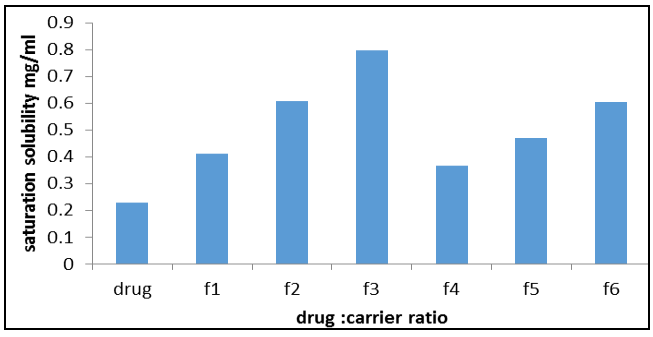

Fig 3: Saturation solubility study of solid dispersion

c. *In-vitro* drug release/dissolution studies:

The *in vitro* release studies were carried out for the Phenytoin solid dispersions prepared by melting method. The dissolution rate of pure Phenytoin was very poor and during 120 min a maximum about 28.55% of the drug was released. The results of in-vitro release studies are given in table no.16 and the graph for percentage cumulative release

are given in Figures 4, 5. The experimentally determined solubility and dissolution of the pure Phenytoin and its solid dispersions in phosphate buffer pH 6.8. All drug-carrier combinations showed an increase in solubility and dissolution of Phenytoin as compared to pure Phenytoin. This might be due to hydrophilic nature of the carriers. Dissolution profiles of all solid dispersion are shown in table no.4 which indicated that the SD ratio 1:3 of drug: PEG 6000 fast dissolution of drug as compared to poloxamer 407. Moreover, improvement of the solubility and the dissolution rate of Phenytoin in its solid dispersion, which can be formulated as tablets or capsules with better dissolution characteristics. The rapid dissolution of Phenytoin from its solid dispersion may be attributed to the decrease in the drug crystallinity and its molecular and colloidal dispersion in the hydrophilic carrier matrix. As the soluble carrier dissolves, the insoluble drug gets exposed to dissolution medium in the form of very fine particles for quick dissolution. The result of drug release in following order F3> F2> F1> F6> F5>F4.showed the dissolution profiles of selected solid dispersions as compared to plain drug. [27-33]

Table 4: In vitro drug release profile of Phenytoin Solid Dispersion with PEG 6000 and Poloxamer 407

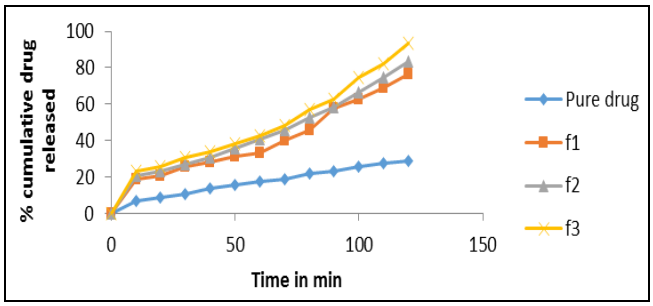

Fig 4: Comparison of pure drug % drug release of solid dispersion with PEG 6000 F1 to F3 batch

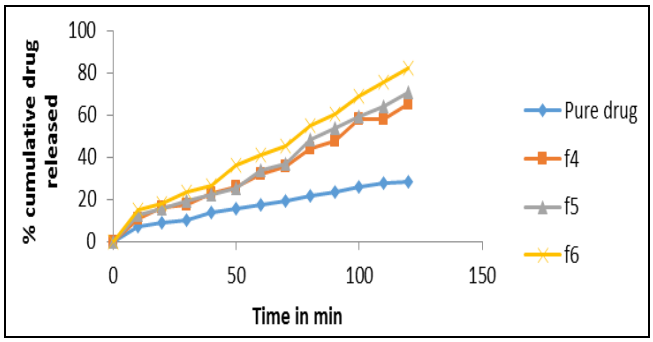

Fig 5: Comparison of pure drug and % drug release of solid dispersion with Poloxamer 407F4 to F6 batch

Conclusion

The enhancement of oral bioavailability of poorly water soluble drugs remains one of the most challenging aspects of drug development. Dissolution of drug is the rate determining step for oral absorption of these drugs, which can subsequently affect the drug's inherent efficacy as a result of irreproducible clinical response. The basic goal of any drug delivery system is to achieve steady state of blood concentration or tissue level that is therapeutically effective and safe for an extended period of time. Currently, only 8.87% of new drug candidates have both high solubility and permeability. Solid dispersions prepared with hydrophilic polymer or surfactants with special physicochemical properties are one of the most attractive approaches to enhance the solubility of a poorly water soluble drug as well as its delivery. From the present study was performed to enhance the dissolution rate and aqueous solubility of Phenytoin, a poorly soluble drug using PEG- 6000 and Polaxamer 407as carrier. Nature and amount of carrier used to play an important role in the enhancement of dissolution rate. Phase solubility study indicates that solubility of Phenytoin increased with polymers concentration. The Negative values of Gibbs free energy indicated spontaneity of transfer. The improvement in solubility can be attributed to effect of polymer. The solubility of Phenytoin in distilled water was found to be (0.10mg/ml); while it was (0.26mg/ml) in pH 6.8. Dissolution of Phenytoin alone was very slow and incomplete up to 120 min. According to the obtained results, only28.49±0.22 % of drug was dissolved after 2 hr. Hence, as the intrinsic solubility as well as rate of drug dissolution is poor, there is strong need to enhance its solubility and dissolution. Solid dispersions prepared with PEG 6000 showed higher solubility and dissolution rate than those pepared with pluronic F-127. Hence, the solid dispersion method, using a hydrophilic carrier such as PEG 6000, could be considered as an appropriate technique for dissolution enhancement of Phenytoin, which is a poorly-soluble drug. Thus, the formulation of solid dispersion of a drug with hydrophilic crriers is a potential approach used to improve the solubility and dissolution rate of practically water insoluble or less soluble drugs.

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