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Development, characterization and solubility enhancement of BCS class II drug phenytoin by solid phospholipid dispersion technique

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ABSTRACT

The poor aqueous solubility acts as a core challenge in oral dosage form development for BCS class II drugs. Phenytoin is taking as a model drug; the present study adopted an innovative solid phospholipid nanoparticle (SPLN) line of attack, and it is parallelly equated with the industrialized methods (freeze-drying) which are used for the boosting of solubility and dissolution of Phenytoin. Phenytoin was articulated along with phospholipid and mannitol at a diverse ratio of phenytoin, PL, mannitol, in which 1:12:18 was the correct ratio for ideal preparation. Freeze-drying helps to prepare SPLNs in orbicular shape, which is amorphous in nature with $\leq 1\mu$m diameter on average. While the amorphous matrix-like structure of solid phospholipid dispersion with larger particle size is obtained by freeze-drying technique. Formulating the formulation from this method improved the dissolution rate in a remarkable way. Tris buffer with pH 7.4acts as an apparent solubility dissolved concentration of phenytoin. The poor aqueous solubility acts as a core challenge in oral dosage form development for BCS class II drugs. The decrease in the particle size or cumulating the drug surface area is the widely used practices to proliferate the solubility. The target of the present work was improvisation in solubility, dissolution of a poorly water-soluble drug, and its release by using solid phospholipid nanoparticles. Phenytoin is taking as a model drug. The solid phospholipid nanoparticles were primed by freeze-drying technique along with phospholipid and mannitol in diverse drug to excipients ratios (1:1, 1:2w: w). These preparations were assessed for compatibility study using FTIR, solubility enhancement study by XRD, entrapment efficiency, surface morphology by SEM, and in-vitro release study. As per the results, there is no influence of the excipients on the drug used. The solubility was increased by folds compared to in house prepared formulation.

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INTRODUCTION

The biggest challenges of API are its poor aqueous solubility and its dissolution rate (Sharma and Kalasare, 2015) in pharmaceutical development, and in past twin decades, this is the most common issue in new drug candidates due to the use of large data and combinatorial screening tools at the phase of drug discovery and selection. As per the pharmaceutical classification system (Buckley *et al.*, 2013). The maximum dose power is not soluble in the aqueous vehicle over the PH ranges at 37° C results in

a drug compound is poorly soluble and most probably such compounds can be seen in class II drug, which has poor water-solubility and high permeability dependent to the PH of the gastrointestinal fluid and may lead to dissolution-limited adsorption (Liu *et al.*, 2010). Regardless of the high permeability of drugs, less oral bio availability due to slow and limited release of drugs in gastrointestinal fluid. Therefore, one of the critical challenges for pharmaceutical industries is to apply drug solubility development in order to convert such problematic compounds into orally bio available and therapeutically effective drugs. To overwhelm the below-par aqueous solubility of drug components have been examined in drug research and development (Balakrishnan *et al.*, 2009) through numerous tactics, and one of them is salt formulation. The pro-drug formation, particle size reduction, Complexation, micro-emulsion, Nano-emulsion, Nano-suspension, solid-liquid Nano-particle (Brinkmann-Trettenes *et al.*, 2014; Brinkmann-Trettenes and Bauer-Brandl, 2014), and solid dispersion that is considered as one of the most successful approaches to expand the dissolution profile of below parsoluble drug (Betageri, 2008). "Solid dispersion (Boral *et al.*, 1995) can be defined as a dispersion of one or more API in an inert carrier or matrix at the solid-state prepared by solvent, melting or solvent melting method". The API in the solid dispersion is dispersed as separate entities (amorphous particle (Babu and Nangia, 2011), molecule, or crystalline particle), whereas the carrier can be in crystalline or amorphous state (Miller *et al.*, 2012). A number of studies regarding the solid dispersion (Chiou and Riegelman, 1971) have been published and have shown numerous advantageous properties of solid dispersion in enhancing the solubility and dissolution rate of poorly water-soluble drug (Gupta *et al.*, 2007). The advantages including reduction in particle size, possibly to the molecular level, enhancing wettability and porosity, as well as the change in the nature of the drug (crystalline state, preferably into the amorphous state) (Frank *et al.*, 2012). In spite of such active research interests, many marketed products produced through solid dispersion techniques (Morgen *et al.*, 2012) is disappointingly low. This can be due to various reasons, mainly during the scale-up process and physicochemical instability during the manufacturing process or during the storage, which may lead to crystallization, phase separation, etc. Very few commercial products have entered the market during the past five decades. Therefore, very deep knowledge that has been acquired on different features of solid dispersions like carrier properties, preparation models (Butler, 1999), characterization of physicochemical methods, pharmaceutical mechanisms of matrix formation, and drug release, which are important to safeguard the preparation of an effective and beneficial solid dispersion for marketing. The objective and aim of the current review are to provide the knowledge from recent approaches on solid dispersion field to overthrow some problems and reasons that ceil the marketability of products through solid dispersion. On the basis of previous literature in this field, the current article newly suggests four classifications of solid dispersions based on the advancement over generation-to-generation have been investigated so far and finally, the possible future frame of reference and approaches of solid dispersions are also discussed.

MATERIALS AND METHODS

Material

Phenytoin was obtained from Sigma Aldrich, (Bangalore). Phospholipid was purchased from SD fine chemical, (Mumbai). Mannitol was procured from Akhil Healthcare private limited (Mumbai), and Tert-butanol was purchased from Ponmani &Company, (Chennai). All other chemical was analytical reagent grade.

Method

Preparation of Phenytoinformulation by Freeze-drying Method

The contents of the various provisions considered in this analysis are shown in the table. A sum of six details was prepared in two fixed matrices (1) freeze-dried physical mixtures (2). For the preparation for the reasons recently evaluated by our meeting. The ratio between phospholipids and mannitol in total was set at 1: 1: 4. Ethanol in water (75:25) by weight and tert-butanol in water (70:30) by weight was the solvent used to dissolve the lyophilization layer separately (Williams *et al.*, 2012).

Physical Blend

Physical mixes of crude material were set up by blending phenytoin, phospholipid, Mannitol utilizing a motor and pestle in 2 distinct arrangements an indicated by theTable 1.

Freeze drying Method

Tert-butanol was first deliquescing in H_20 proportion of (70:30, w/w), phenytoin, phospholipid, Mannitol was dissolving in the solvent blending to as indicated by the individual organization depicted. Formulation blending under magnetic storm mixing

Table 1: Composition of Studies formulation

Formulation Code	Production Method	Composition(Mass)			Solvent
		Drug	PLs	Mannitol	
PB1	Physical blends	1	0	0	Nil
PB2	Physical blends	1	2	6	Nil
PB3	Physical blends	1	4	12	Nil
FD1	Freeze drying	1	2	6	Tert-butanol in water
FD2	Freeze drying	1	4	12	Tert-butanol in water
FD3	Freeze drying	1	12	18	Tert-butanol in water

for 30mins. The formulation was by then freezes at -80ºc for 24 hrs. before set pre-cooled freeze dryer -60ºc. lyophilization was performed by the as indicated by the venture a standard drying stage with rack temperature at 25ºc and weight of 0.1 mbar for 24 hrs. pursued by last drying stage with rack temperature at 25ºc and weight 0.01 mbar for 4hrs. the rest of the substance of common deliquesce was controlled by weighing the sample vials when freeze-drying and was seen to the worthy. ($\leq$ 1%) the vials were fixed and put away at room temperature in a desiccator above calcium chloride the investigation (Desobry *et al.*, 1997; Fong *et al.*, 2015).

Structural analysis

The essential structure studies of phenytoin and the diverse plans were finished by an X-ray diffractometer with Cu Kα radiation (1=1.5418 A). the power test was predicated inside the long range of 14-17º 2Ø, with a stage measure of 0.02 beneath the consequents condition stream 11mA, Voltage 40 kV looking at speed 10º 2Ø /mines (Galia *et al.*, 1998).

Particle Morphology

The morphology of the phenytoin particles and the different formulations were examined using a scanning electron microscopy with the corresponding parameter. Check the currents at 45 pA and the voltage at 22,000 eV. During the test, a thin layer of gold (20 nm) was closed to improve electrical conductivity using a molecules sputter coater of JEOL.

Solubility and dissolution studies

Preparation of media

Phosphate buffers (PBS pH 7.4) were utilizing the media for solubility and dissolution thinks about. Two were set up within the though with the approaches proposed for the maker. For the status of the PBS (phosphate buffer saline) formula and planning plan, 800ml of distilled water in an appropriate holder includes 8g NaCl to the solution. Include 200mg of KCL to the solution. Include 1.44g of Na_2Po4 to the solution. Include 240mg of KH2Po4 to the solution (Faller and Ertl, 2007).

Dissolution studies

Dissolution 0.05M Tris buffer dissolving 36.3g of tris (hydroxyethyl) aminomethane and 60g of sodium lauryl Sulphate in 6ml water alter with hydrochloric acid to a pH of 7.4 $\pm$ 0.05 and degas. Medium: 0.05M Tris buffer 900ml, dissolution test was performed utilizing a USP type 2 device within 900ml, shake the sample suspension well, around 100 shakes Utilizing a5ml syringe. Accumulate around 5ml of suspension and record the weight. With the paddle brought down gently, clear the substance of each syringe into the base of each vessel containing the medium start turning the paddle, reweigh each syringe, and chose the degree of suspension passed on into each vessel. Toward the wrap up of an hour, remove 4ml. from each vessel and pass through that be μm nylon screen pre-soaked with the medium.

Thermodynamic and apparent solubility Studies

The solubility of phenytoin in PBS buffer pH 7.4, as well as the reasonable solubilities[13] of phenytoin, physical mix and freeze-drying formulation within the isolated medium (PBS 7.4), were given by the shake flask container method, overabundance (12 Mg amount of drug) of phenytoin physical mix, formulating were scattered a 4.5ml of the person halfway. These shaking testing was shower (Julabo SW 23 bunch and holm, Demark) and programmed shacked the permitted a 100 rpm until assentation was come to upon adjusting (in the 7day appeared by crucial studies) the test was centrifuged an 11,000 rpm of 1 hrs. to isolate the strong undissolved stage. So they supernatant was a channel through a 0.45μm channel was sometime recently investigating by HPLC all examination was performed in triplicates (Behera *et al.*, 2010).

Analytical Method

HPLC/UV was utilizing this estimation of the drug in all inspecting. Chromatographic segment was

reached be a turnaround organized approval C_1 section (149mm x 4.8mm for example 3μm particle degree, Thermo fisher) outfitted with approval screen channel (5μm, Thermo fisher) based to our supported procedure (Information not appeared up) isocratic elution with flexible organize including 0.1% formic acid: ethanol (18:82) as the stream rate of the 1ml/min were utilizing and they stove temperature was set up 30ºc. UV of phenytoin setting up 256nm.

RESULTS AND DISCUSSION

The standard plot of Phenytoin in o.1 M Tris buffer

Standard curve of the phenytoin drug was developed, and the perfect correlation was observed from the regression value (R^2= 0.9989) Figure 1 and it shows that the perfect linearity between the concentration and absorbance was observed when the concentration range was from 2μg/ml to 10μg/ml.

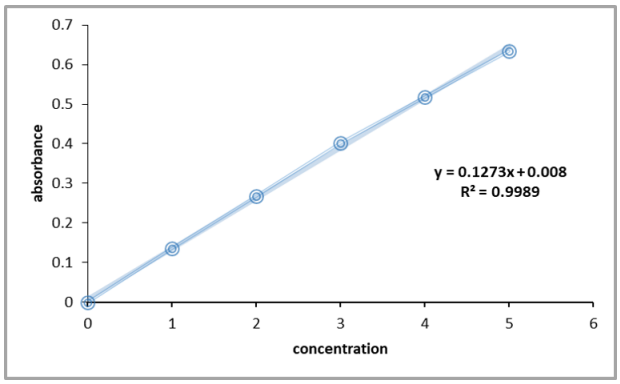

Figure 1: Standard curve of phenytoin

Compatibility studies

FT-IR studies

Fourier transform infrared spectroscopy was performed to check the compatibility between the drug phenytoin and excipients Table 2. The spectra obtained from IR studies are the length from 4000cm-1 to 400cm-1. After the interpretation, it was observed that no functional group loss in between the spectra of drug and excipients, no major shifting of peak occurred. FT-IR spectra of phenytoin, phenytoin formulation, the physical mixture was shown in Figures 2, 3 and 4.

Structural analysis

By defining crystalline phenytoin with phospholipid and mannitol using the method freeze-drying upon all-out dissolution of the mixes, it is foreseen that an amorphous state would be created. X-beam powder diffraction was working to look at the degree of crystallinity of the crystalline and crude phenytoin.

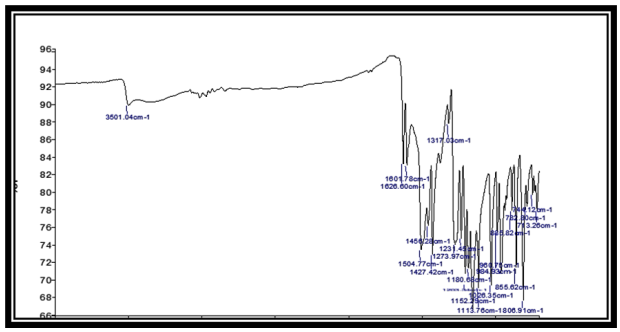

Figure 2: FT-IR spectra of phenytoin

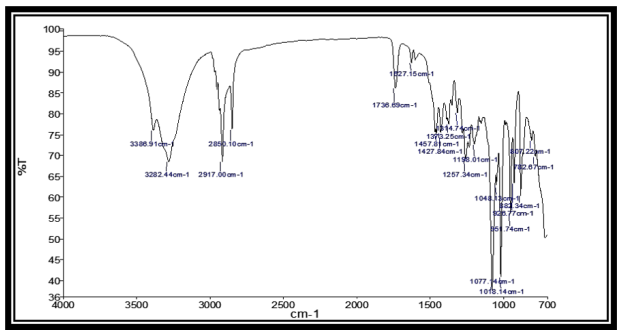

Figure 3: FT-IR spectra of phenytoin Formulation

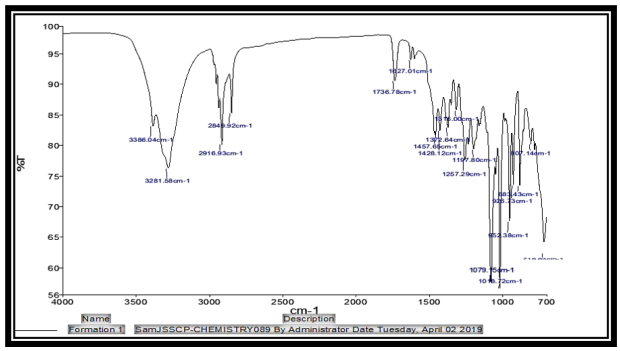

Figure 4: FT-IR spectra of Physical Mixture

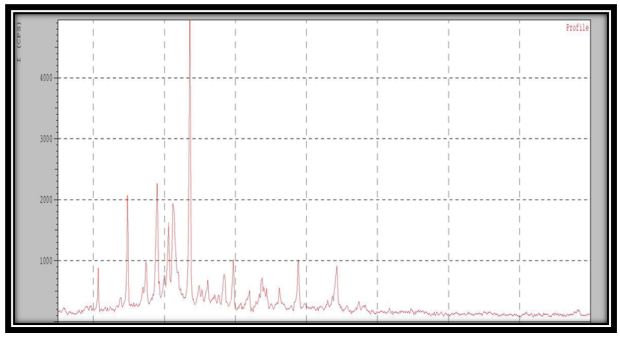

Figure 5: X-ray diffract gram of Pure drug (Phenytoin)

Table 2: FT-IR interpretation of pure drug, Formulation, Physical Mixture

Material	Standard wave Number (cm^{-1})	Test wave Number (cm^{-1})	Functional Group assignment
Drug, Formulation, Physical Mixture	2800-3500	3281.58	OH Stretching
	900-1500	1257.29	C-O Stretching
	750-900	883.43	C-H Bend
	1500-1700	1601.78	C=C stretching
	2700-3300	3014.01	C-H stretching

Table 3: Dissolution profile pH 7.4

S.No	Time (min)	Percentage of drug release (%)		
		Pure Drug	F1	F2
1.	0	0	0	0
2.	5	20	52	65
3.	10	25	63	73
4.	15	28	69	78
5.	30	29	73	84
6.	45	30	78	89
7.	60	35	85	95

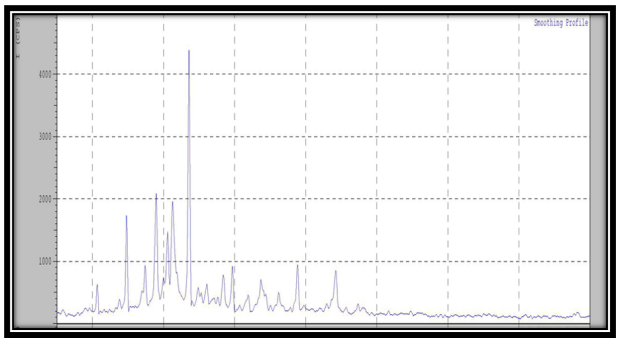

Figure 6: X-ray diffract gram of Physical Mixture

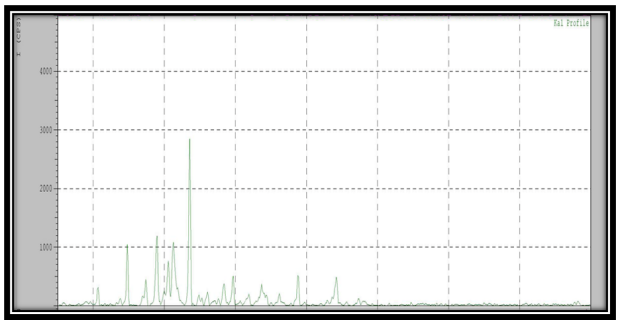

Figure 7: X-ray diffract gram of Freeze-dried Formulation

The X-beam diffract gram of the rough phenytoin showed incredibly trademark apices at 2ø extended from 20 to 30º, demonstrating the crystalline idea of phenytoin. After freeze-drying with phospholipid and Mannitol at the various drug and excipient proportions, the X-beam diffract gram showed a trademark crest less paradigm. this showed phenytoin was molecularly scattered inside the Phospholipids in these formulations, in this manner making strong amorphous scattering in all cases. X-ray diffract gram of Pure drug (Phenytoin), physical mixture, Freeze-dried Formulation was shown in Figures 5, 6 and 7.

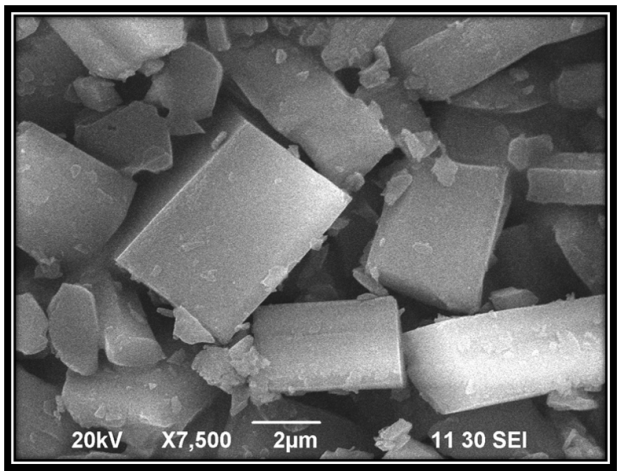

Figure 8: Scanning electron microscopy of Phenytoin

Particle Morphology

Scanning electron microscopy was performed to analyses the surface morphology of rough phenytoin, the formulation of lyophilization with phenytoin, phospholipid, the composition of mannitol 1:12:18. From Figures 8, 9 and 10. The crude

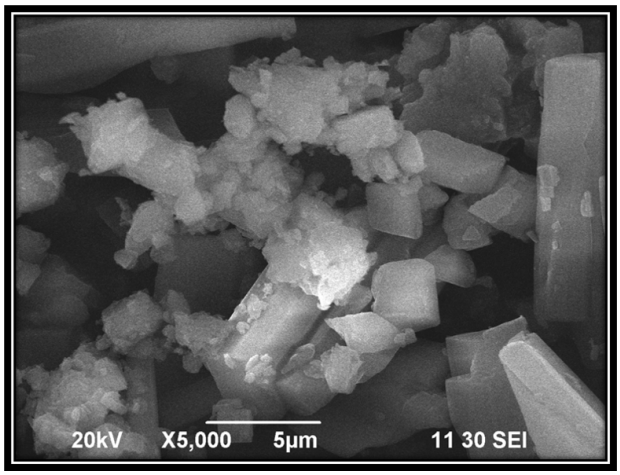

Figure 9: Scanning electron microscopy of physical mixture

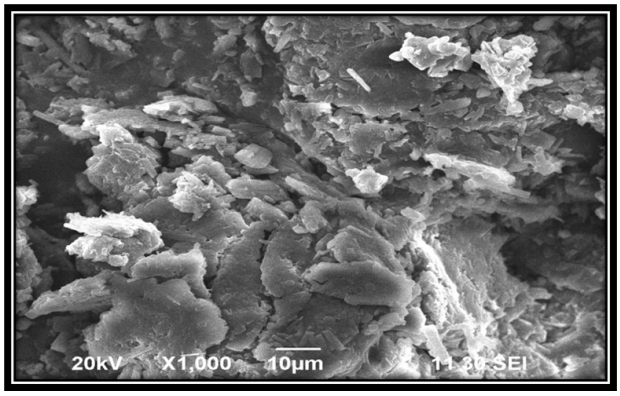

Figure 10: Scanning electron microscopy of Freeze-dried Formulation

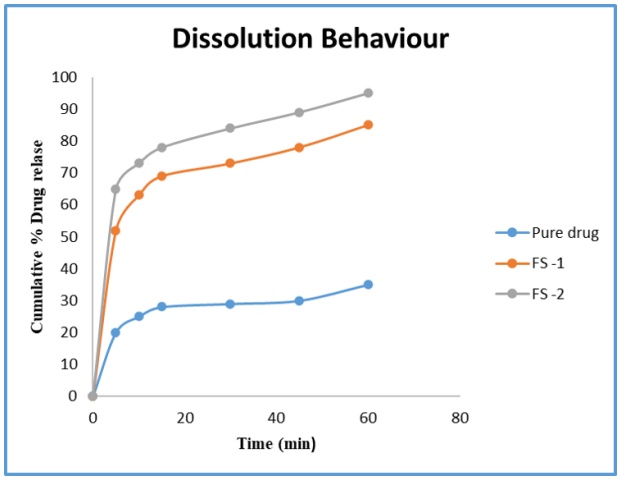

Figure 11: Dissolution profile of phenytoin in freeze-dried formulation with phospholipid and mannitol different ratio phosphate buffer saline pH 7.4 studies were performed using USP type 2 apparatus at 50rpm in 900ml

phenytoin seemed, by all accounts, to be crystalline and needle-molded with a length of around 10 gm. The watched crystallinity of phenytoin is in concurrence with our X-beam diffractogram result, and with the perception of, the lyophilization formulation demonstrated a round morphology with a distance across running from a few miniaturized micrometers up to the Nano run (less than 1 gm). Amorphous SPLNs[26] have been effectively made by the formulation of phenytoin with phospholipids and mannitol utilizing a lyophilization technique. As of late depicted by our gathering. Then again, it appeared to have a structure like an amorphous network with a lot bigger grain size.

Dissolution studies in pH 7.4 (PBS)

In vitro release study was performed at a pH of 7.4. Determination of in vitro dissolution was carried out using Drug, Formulation, and phosphate buffer (pH 7.4), and the drug release of all three was observed in 60 min. The % cumulative drug release data of all samples were shown in Table 3 and Figure 11. The results indicated that the % cumulative drug release of FS-2 formulation was found to be 90% after 60 minutes.

Solubility Studies

The apparent solubility studies have been performed for Pure drug, FS-1, and FS-2. They all are having a different-different concentration of solubility. Pure drug (phenytoin) is having a concentration of 1μg/ml, FS-1 is having a concentration of phenytoin is 30μg/ml, and FS-2 is having a concentration of phenytoin is 50μg/ml. The apparent solubility data of phenytoin is shown in Table 4 andFigure 12.

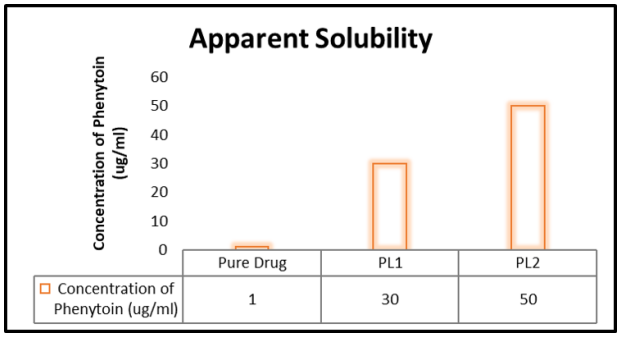

Figure 12: Apparent solubility studies

CONCLUSION

Solid phospholipid dispersion techniques for BCS class II drugs like phenytoin, which enhances the solubility of the drug for their oral dosage form. In the behave of Scanning electron microscopy, x-ray diffraction, dissolution studies, and compatibility studies and lyophilization to estimated their physio-

Table 4: Solubility Studies pH 7.4

S.No	sample	Concentration of phenytoin(μg/ml)
01.	Pure drug	1
02.	FS-1	30
03.	FS-2	50

chemical property of phospholipid drug, which becomes a promising approach for the bioavailability.

Conflict of interest statement

The authors declare that there are no conflicts of interest in this study. The authors alone are responsible for the content and writing of the paper.

Author's contribution

Sathish Ananthan was the lead author and synthesized the literature. Veera Venkata Satyanarayana Reddy Karri provided conceptual inputs. Lavanya Mude involved in drafting the paper, critical revision of the manuscript. All authors read and approved the final paper.

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REFERENCES

Babu, N. J., Nangia, A. 2011. Solubility Advantage of Amorphous Drugs and Pharmaceutical Cocrystals. *Crystal Growth & Design*, 11(7):2662–2679.

Balakrishnan, P., Lee, B. J., Oh, D. H., Kim, J. O., Hong, M. J., Jee, J. P., Choi, H. G. 2009. The enhanced oral bioavailability of dexibuprofen by a novel solid self-emulsifying drug delivery system (SEDDS). *European Journal of Pharmaceutics and Biopharmaceutics*, 72(3):539–545.

Behera, A. L., Sahoo, S. K., Patil, S. V. 2010. Enhancement of solubility: a pharmaceutical overview. *Der Pharmacia Lettre*, 2(2):310–318.

Betageri, G. V. 2008. Enhancement of the dissolution of poorly water-soluble drugs using proliposomes. *American Pharmaceutical Review*, pages 11–11.

Boral, A., Sen, N., Ghosh, G. B. K. 1995. Solid dispersion technology for controlling drug release and absorption. *The Eastern Pharmacist*, pages 141–143.

Brinkmann-Trettenes, U., Barnert, S., Bauer-Brandl, A. 2014. Single-step bottom-up process to generate solid phospholipid nano-particles. *Pharmaceutical Development and Technology*, 19(3):326–332.

Brinkmann-Trettenes, U., Bauer-Brandl, A. 2014. Solid phospholipid nano-particles: Investigations into the formulation and dissolution properties of griseofulvin. *International Journal of Pharmaceutics*, 467(1):42–47.

Buckley, T., S., Frank, J., Fricker, K., Brandl, G. 2013. Bio pharmaceutical classification of poorly soluble drugs with respect to "enabling formulations. *European Journal of Pharmaceutical Sciences* , 50:8–16.

Butler, J. M. 1999. Method producing a solid dispersion of poorly water-soluble drugs. *United States Patent*, 985(5). Patent and Trademark Office.

Chiou, W. L., Riegelman, S. 1971. Pharmaceutical Applications of Solid Dispersion Systems. *Journal of Pharmaceutical Sciences*, 60(9):1281–1302.

Desobry, S. A., Netto, F. M., Labuza, T. P. 1997. Comparison of Spray-drying, Drum-drying, and Freeze-drying for β-Carotene Encapsulation and Preservation. *Journal of Food Science*, 62(6):1158–1162.

Faller, B., Ertl, P. 2007. Computational approaches to determine drug solubility. *Advanced Drug Delivery Reviews*, 59(7):533–545.

Fong, S. Y. K., Brandl, M., Bauer-Brandl, A. 2015. Phospholipid-based solid drug formulations for oral bioavailability enhancement: A meta-analysis. *European Journal of Pharmaceutical Sciences*, 80:89–110.

Frank, K. J., Rosenblatt, K. M., Westedt, U., Hölig, P., Rosenberg, J., Mägerlein, M., Brandl, M. 2012. Amorphous solid dispersion enhances the permeation of poorly soluble ABT-102: True supersaturation vs. apparent solubility enhancement. *International Journal of Pharmaceutics*, 437(1):288–293.

Galia, E., Nicolaides, E., Hörter, D., Löbenberg, R., Reppas, C., Dressman, J. B. 1998. Evaluation of Various Dissolution Media for Predicting In Vivo Performance of Class I and II Drugs. *Pharmaceutical Research*, 15(5):698–705.

Gupta, V., Mutalik, S., Patel, M., Jani, G. 2007. Spherical crystals of celecoxib to improve solubility, dissolution rate, and micrometric properties. *Acta Pharmaceutica*, 57(2):173–184.

Liu, Y., Sun, C., Hao, Y., Jiang, T., Zheng, L., Wang,

S. 2010. Mechanism of dissolution enhancement and bioavailability of poorly water-soluble celecoxib by preparing stable amorphous nanoparticles. *Journal of Pharmacy & Pharmaceutical Sciences*, 13(4):589–606.

Miller, J. M., Beig, A., Carr, R. A., Spence, J. K., Dahan, A. 2012. A Win-Win Solution in Oral Delivery of Lipophilic Drugs: Supersaturation via Amorphous Solid Dispersions Increases Apparent Solubility without Sacrifice of Intestinal Membrane Permeability. *Molecular Pharmaceutics*, 9(7):2009–2016.

Morgen, M., Bloom, C., Beyerinck, R., Bello, A., Song, W., Wilkinson, K., Shamblin, S. 2012. Polymeric Nanoparticles for Increased Oral Bioavailability and Rapid Absorption Using Celecoxib as a Model of a Low-Solubility, High-Permeability Drug. *Pharmaceutical Research*, 29(2):427–440.

Sharma, P. H., Kalasare, S. N. 2015. Poorly soluble drugs - A challenge in the drug delivery system. *European Journal of Pharmaceutical and Medical Research*, 2:484–502.

Williams, R. O., Watts, A. B., Miller, D. A. 2012. Formulating Poorly Water Soluble Drugs. pages 311–362, New York. Springer Cham. ISBN: 978-3-319-42609-9.