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Development of Phenytoin Preparation Using Liquid Solid Compact Technology

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ABSTRACT

Epilepsy is a very common disease, characterized by unconsciousness, which takes a variety of forms and causes episodic neuronal discharge, a type of fainting depending on the part of the brain affected. There is no cause of recognition, although it may develop after a mental injury, such as trauma, infection or trauma, or other neurological diseases. Epilepsy is most commonly treated with drugs, although brain surgery may be used in extreme cases. Sodium channel blockers are commonly used to treat seizures, EG-. Phenytoin, carbamazepine, sodium valproate. This study aimed to develop a matrix tablet for the continuous release of phenytoin using, polyethylene glycol 400, methylcellulose pH 200, sodium alginate, propylene glycol, span 80, tween 80, lactose anhydrous, sodium starch glycolate, magnesium stearate and talc powder as the regulatory factor release. And exploring drug release parameters as various kinetic models. The built-in pills were also available characterized by physical and chemical parameters and results were obtained within acceptable limits. A different finish model used in drug release data to evaluate release modes and kinetics. Terms of choice the most appropriate model was based on line (coefficient of correlation). Based on the value of "n" (0.168) tree the release followed the Ficki distribution. And the drug release method is best described by Higuchi's order (composite value is 0.9063) using this polymer.

Keywords: Epilepsy, Bioavailability, Compatibility, Pheny

INTRODUCTION

Bioavailability

It is defined as the amount of drug or active moiety is available or enter in the systemic circulation is called the bioavailability. There are the two important parameters in bioavailability are:

- Solubility
- Permeability

Solubility: It is defined as the amount of drug that is soluble in the body and shows the therapeutic effect in the body is called the solubility.

Permeability: It is defined as the ability of the drug to pass through the biological membrane is called the permeability (Table 1).

Table 1 Biopharmaceutical Classification System (BCS)

Class	Permeability	Solubility
Class 1	High	High
Class 2	High	Low
Class 3	Low	High
Class 4	Low	Low

Problems

In BCS class 2 drugs the solubility of the drug is very low and the bioavailability of the drug is poor so the drug is not take part in the systemic circulation and does not show a therapeutic effect in the body.

To solve this problem there are several methods to overcome the solubility of the drugs.

Liquid solid compaction technique: this is the technique of conversion of the liquid material into the dry form with the help of the excipients and the coating materials.

Many of the pharmaceutical ingredients is one of the technological challenges in the proper construction volume form for optimal use. More than 40% recently the chemical associations built in the pharmaceutical industry are almost insoluble in water.

- When combined with features of in vitro termination of drug product, The Biopharmaceutical Classification System (BCS) calculates three major factors: melting, intestinal invasion, and the level of completion, all dominating the level and level of this the absorption of oral drugs in the sustained release of solid oral dose forms.
- With BCS Phase II drugs, the process of dissolution is a measure control measure, which determines the level and level its absorption.
- "Liquid solid compact technology" has succeeded as a tool to improve melting and dehydration soluble drugs and consequently bioavailability. The solid-liquid system refers to the structure formed by liquid drug conversion, drug suspension, or drug solution to soluble solvents, into dry, adhesive, flowing, and compact mixtures by combining suspension or solution.

Methods to resolve the problem related to solubility are:

Liquid Solid Compact Technique

In this technology, we use the solid as a core material in which the liquid or viscous solution is mixed with the solid and forms a complex mixture. The complex mixture is passed with the sieve and for the granules.

Liquid Solid Compact Technology Details

Liquid solid compacts are used to make water-soluble drugs in soluble solvents and convert them into pressurized flow powders that are acceptable in combination with selected powder powders. By using this method, the level of dissolution and bioavailability of BCS class-II drugs can be increased. About 40%-50% of the available drugs are soluble in water. It is a challenge for the industry to increase the melting of unit volume forms to overcome this solid-liquid technology which is the most suitable. In this study pre-assembled parameters such as porosity, corsality index, flow behaviour, power bed hydrophilicity, and saturate melting. Post-pressure parameters are similar in similarity, weight variation, hardness, durability, wetness, and duration. For this, we can use carrier (microcrystalline cellulose, starch, and lactose), dressing (silica gel), and dividing agents. In this case, we can convert infrared spectroscopy, Differential Scanning Calorimeters (DSC), and a separate scanner, x-ray diffraction (Figure 1).

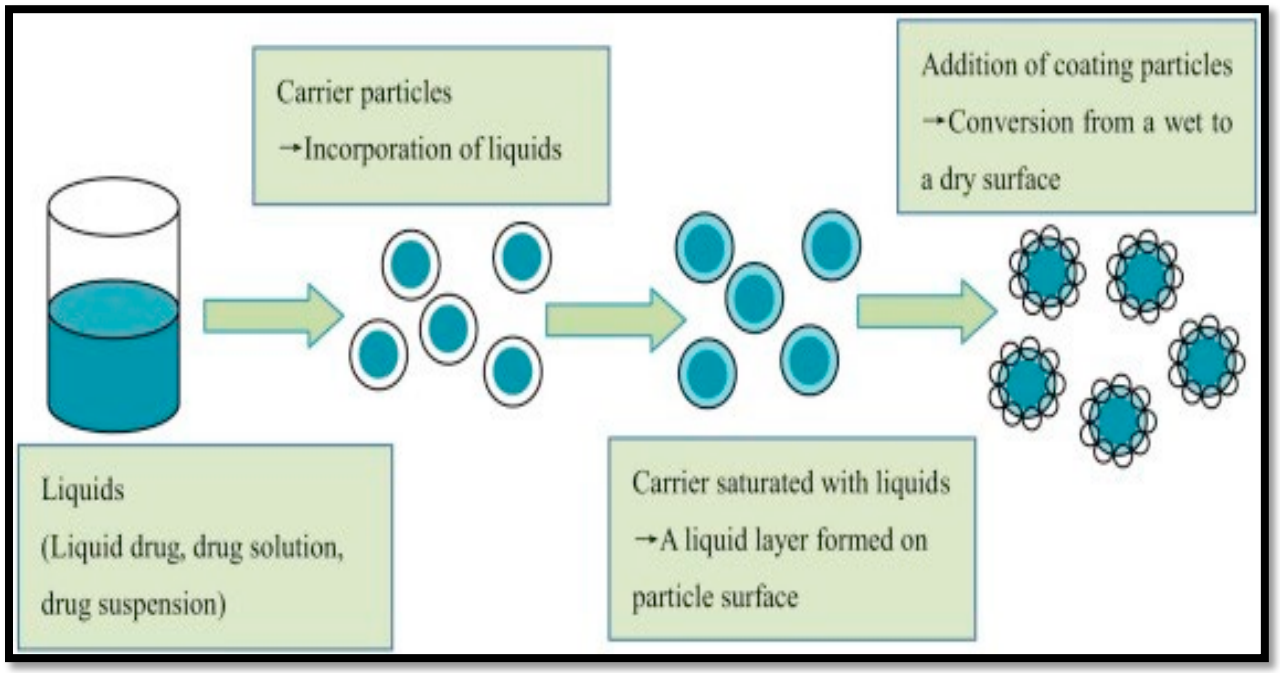

Figure 1 Method of building a liquid-solid system [4]

Theory of Liquid Solid System

The powder can retain a limited amount of liquid medicine while maintaining acceptable flow and pressure. Therefore, in order to achieve a liquid solid system with acceptable flow and pressure structures, the anatomical model.

The carrier is filled with liquid. The liquid layer on which it is built particles on the surface Addition of wear particles Conversion from wet to dry place presented and verified by Spireas it is recommended to calculate the appropriate amounts of cargo and cover items. The model is based on two basic elements of powder, i.e., the ability to retain a liquid flow (Φ value) once the storage capacity of the pressurized fluid (Ψ value). Φ and Ψ the powder receiver values represent the maximum amount of liquid vehicle that can be stored in bulk powder. Without compromising flow and compression.

The Φ value is best determined by measuring the angle of the slide of the prepared liquid-powder mixture. Num Ψ value can be measured by a test called plasticity, i.e. is described as the high crushing power of a tablet with the weight of a one-gram tablet when pressed with sufficient pressure [1-4].

The Excipient ratio (R), also known as carrier/coating rate, is defined as:

$$R = Q/q \quad (1)$$

Therefore, R is the ratio between the weights of a carrier (Q) and coating material (q). There will be an increase of R leading to higher carrier value and lower costs of cover material. As the value of R is associated with the flow and pressure of structures, dispersion, and the dispersion rate of the liquid-solid system, a large amount of R is recommended to be 20. Another important parameter of the liquid-solid system is called the liquid loading element (Lf), defined as the mass of liquid medications (W) and administration (Q) in a liquid-solid system.

$$\boldsymbol{L_f = W/Q} \quad (2)$$

Liquid loading element for liquid-solid production in a system with an acceptable flow can be determined by:

$$\boldsymbol{L_f = \Phi + \phi/R} \quad (3)$$

When **Φ** and **ϕ** values correspond to the flow fluid the company's ultimate power and network coverage, with respect. Consistently, the liquid loading feature guarantees acceptable pressure of the liquid-solid system can be defined as:

$$L_f = \Psi + \psi/R \quad (4)$$

Where Ψ and ψ values correspond to the pressure storage capacity of carrier fluids and coverings, respectively. Therefore, the optimum liquid loading factor (L_0) which produces a liquid solid system with an acceptable flow and congestion is equivalent to ΦL_f or ΨL_f, anywhere has a low value.

Since Φ, Ψ, ϕ, and ψ values are the constant elements of each powder a mixture of liquid, according to the given excipients ratio (R), preferably liquid loading factor (L_0) can be calculated according to equations (3) or (4). Then, depending on the different drug addiction, different weights of the liquid drug (W) will be used. So, based on calculated L_0 and W, fair value the appropriate amount (Q_o) and Coating material can be calculated according to the equation 1 and 2, respectively.

ADVANTAGES

Many of the benefits of the liquid-solid method have been re-reported.

- Large amounts of water melting slowly, very slowly Water-soluble and water-soluble drugs can be synthesized into liquid-solid systems with improved solubility and bioavailability.
- Construction of a stable release with zero order the release pattern can be achieved as long as hydrophobic carriers, such as Eudragit® RL and RS, or similar retrieval agent's Hydroxyl Propyl Methyl Cellulose (HPMC) used in liquid-solid programs.
- This process has the potential to produce liquid solid tablets or pills with pH-independent drug release profiles.
- It is another promising method of general integration how to improve the photostability of drugs in a stable environment volume forms.
- Installed equipment is readily available and economical. Besides, the preparation process is simple, similar to the usual solid dosage forms (i.e. tablets and capsules). In addition, the good flow and pressure of the liquid powder make the process more productive [5-13].

DISADVANTAGES

There are several disadvantages associated with the liquid-solid technique.

- The method is used effectively at low-volume drugs that do not dissolve in water, while the inclusion of large doses of water-soluble drugs into liquid-solid systems is its main limit. As these drugs require a lot of liquid vehicles, therefore, to obtain liquid solid powder in good flow and oppressive structures, a large number of carriers, as well as adhesive material, is required. This may increase the weight of the tablet beyond the limit, which is difficult for patients to swallow. Several Strategies have been reported to address the above barrier. For example, adding other additives (i.e., PVP and PEG 35000) in liquid medicines increasing viscosity can decrease the quantity of bearing materials and adhesives. Additionally, the use of modern network company assets and coverage (e.g. Fujicalin® and Neusilin®) with a large specific area (SSA) and high absorption capacity is another effective way to load a large amount of soluble drugs in water.
- A High solubility of the drug in the liquid vehicle is required to prepare liquid-solid systems [14].

MATERIALS AND METHODS

Material: Phenytoin, Microcrystalline Cellulose Ph. 200, Sodium Alginate, Polyethylene Glycol 400, Propylene

Glycol, Span 80, Tween 80, Lactose Anhydrous, Sodium Starch Glycolate, Magnesium Stearate and Talc these entire chemical is provide by the drug store.

Methods: The solubility of the water and the three liquid vehicles are used to prepare the liquid solid system propylene glycol, polyethylene glycol 400 and tween 80 are mixed properly and formed the saturated solution analysed the spectrophotometrically. The mixture is sonicated for one day and cooled then 25°C under constant vibration

Preparation of Liquid-Solid Tablet

Calculated quantities of phenytoin and PEG 400 were accurately weighed in a 20 ml glass beaker and sonicated at a controlled temperature (80°C to 90°C) until a homogenous solution was obtained. The appropriate amounts of carrier and coating materials used for each formulation depend upon the Lf of that formulation. A mixture of microcrystalline cellulose pH 200 and sodium alginate was added to the above liquid medication under continuous mixing in a mortar. Sodium starch glycolate was added to the above binary mixture and mixed for a period of 10 min to 20 min. Talc and magnesium stearate were added to the mixture and mixed for 2 min. The resulting liquid-solid material was evaluated for followability and compressibility. The liquid-solid mixture was compressed into a tablet using an 8 mm punch and die set in a tablet compression machine. The liquid-solid tablets were evaluated for appearance, weight variation, hardness, friability; disintegration time, content uniformity, and drug release (Table 2 and Figure 2).

Table 2 Formulation of liquid-solid tablets

Phenytoin	PEG 400	Methylcellulose	Sodium Alginate	Magnesium Stearate	Sodium Starch Glycolate	Talc Powder
400 mg	0.88 ml	1 gm	800 mg	1 gm	1 gm	1 gm
400 mg	0.88 ml	2 gm	800 mg	1 gm	1 gm	1 gm
400 mg	0.88 ml	3 gm	800 mg	1 gm	1 gm	1 gm
400 mg	0.80 ml	1 gm	800 mg	1 gm	1 gm	1 gm
400 mg	0.80 ml	2 gm	800 mg	1 gm	1 gm	1 gm
400 mg	0.80 ml	3 gm	800 mg	1 gm	1 gm	1 gm
400 mg	0.72 ml	1 gm	800 mg	1 gm	1 gm	1 gm
400 mg	0.72 ml	2 gm	800 mg	1 gm	1 gm	1 gm
400 mg	0.72 ml	3 gm	800 mg	1 gm	1 gm	1 gm

Evaluation of the tablet: The finished products were evaluated as per the procedures given in USP I which recommends the following tests for sustained-release tablets.

Weight variation test: The weight variation test was performed on the 20 tablets as per the USP. Where weight using electronic balance and the average weight is calculated each tablet was weighed individually and weight was noted. The weight of individuals where compare to the average weight and the mean and standard deviation.

Hardness test: For each formulation, the hardness of 6 tablets was determined using the hardens tester like Monsanto hardness tester and ultrasonic hardness tester. The hardens value was reported in kilograms and calculated the mean and standard deviation.

Friability test: For each formulation, 6 tablets are weight for before test and noted down put all the 6 tablets in a friability test like Roche friabilator and start the machine rotate out for 4 minutes in 1 minutes take 25 rpm total 100 rotations. The Tablets are taken out in weight noted down the weight. Calculated the percentage of loss weight.

$$\% \text{ Friability} = (\text{loss of mass/Initial mass}) \times 100$$

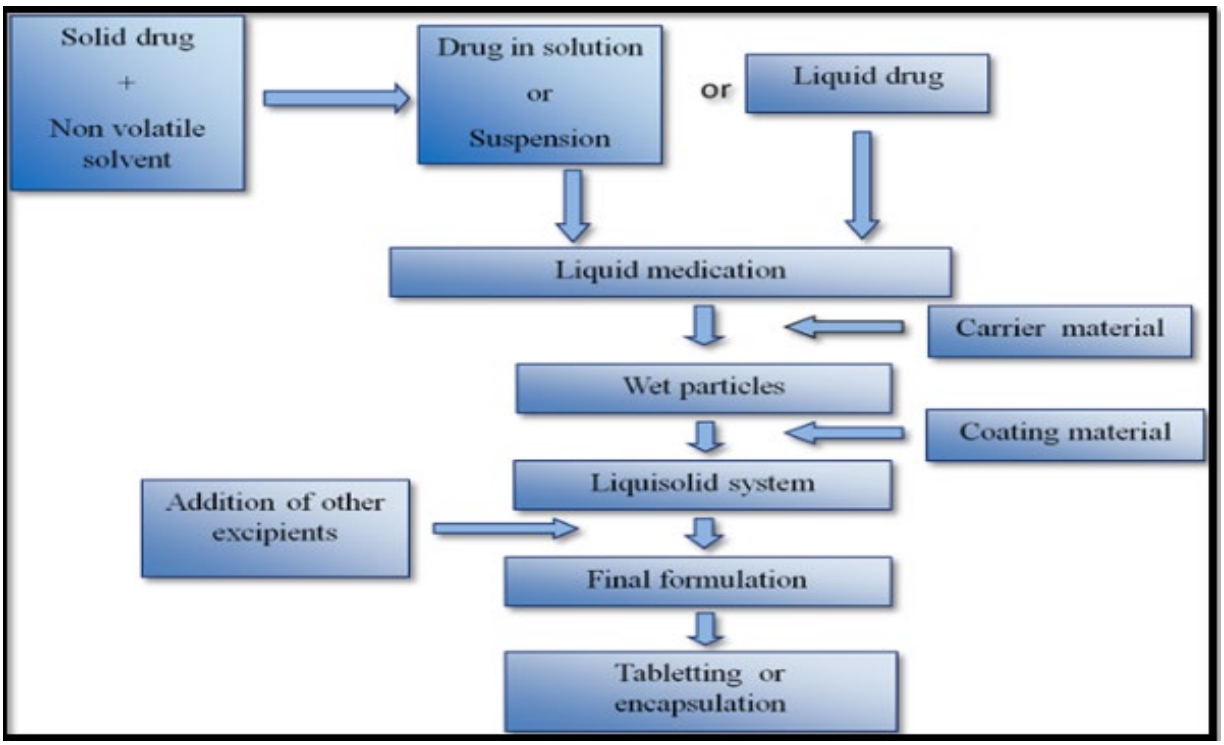

Figure 2 Preparation procedure of liquid-solid system [21]

Disintegration test: Disintegration tests are performed for each of the 37˚C ± 1˚C in distilled water six tablets in each formulation using the tablet disintegration unit. The tablets were considered completely dispersed no remains on screen. Generally, a good tablet hardness should be produced without the use of excessive compression force where the tablet disintegrates rapidly and drug termination is maintained at the same time.

Content Uniformity

For each formulation, 10 tables in each group were taken randomly for testing content uniformity. Each tablet was weighed and crushed individually. Crushed tablet powder is melted in the middle of methanol. The solution was filtered using a Whatman filter paper. The drug content was measured using a UV spectrophotometer at 242.6 nm. According to the British Pharmacopoeia Percentage of individual drug content is calculated against the average drug content [15-20] (Table 3).

Table 3 Physical parameters of liquid-solid tablet

Liquid Solid System	Hardness (kg/cm^2)	Disintegration Time (sec)	Friability (%)	Weight Variation (Mg)	Content Uniformity (%)
Ls 1	2.3 ± 035	14 ± 0.28	0.18	238 ± 0.45	99 ± 0.42
Ls 2	2.7 ± 035	14.5 ± 0.23	0.21	243 ± 1.55	97.51 ± 0.25
Ls 3	3.1 ± 0.41	15 ± 0.32	0.3	216 ± 0.93	95.27 ± 0.15
Ls 4	3.9 ± 0.14	15.9 ± 0.45	0.37	310 ± 1.29	98.21 ± 0.50
Ls 5	4.2 ± 0.88	16.5 ± 0.51	0.44	341 ± 1.96	98.60 ± 0.45
Ls 6	4.6 ± 0.31	17.4 ± 0.26	0.49	380 ± 1.77	97.26 ± 0.23
Ls 7	4.5 ± 0.35	18.6 ± 0.18	0.53	405 ± 0.49	96.51 ± 0.44
Ls 8	3.8 ± 0.28	19 ± 0.35	0.57	462 ± 1.20	98 ± 0.20
Ls 9	4.8 ± 0.22	20.2 ± 0.15	0.65	483 ± 1.40	99.25 ± 0.24

In Vitro Release Studies

In vitro release studies of phenytoin sustained release tablet was monitored the experiment was performed on a 900 ml dissolution medium of hydrochloric acid pH was maintained at 1.2 for the first 2 hours and then replaced with the same volume of phosphate buffer solution was pH maintained at 6.8 at 37°C and stirred at 100 rpm using the usp1 basket dissolution apparatus in perfect sink condition the 5 ml sample was withdrawn through a 0.45-micrometer filter and replace with another 5 ml.

Applications of liquid-solid techniques

To enhance the drug dissolution: Based on the literature, liquid-solid technique has been widely used to improve the dissolution rate of low-dose insoluble drugs, such as prednisolone, famotidine, valsartan, ketoprofen, raloxifene hydrochloride, clonazepam, clofibrate, etc. In the case of high-dose water-insoluble drugs (i.e., carbamazepine), the feasibility of the liquid-solid technique has also been discussed. Javadzadeh et al. suggested that it is possible to involve the liquid-solid technique in the incorporation of high-dose water-insoluble drugs into liquid-solid systems by adding some additives (such as PVP, HPMC, and polyethylene glycol 35000), because these additives have the capability to increase the liquid absorption capacity of carrier and coating materials. Hentzschel et al. have shown another potential approach to load high doses of poorly water-soluble drugs into liquid-solid systems, namely by using modern carriers (such as Neusilin®) with larger SSA value and higher absorption capacity [21-23].

Used as a tool to sustained release: The solubility of weak acids and bases is dependent on the ionization constant (pKa) of the compound and pH of the local environment. Therefore, the dissolution and bioavailability of these drugs are greatly influenced by the pH of gastrointestinal fluids. This further leads to a high degree of inter- and intra-availability in drug bioavailability and therapeutic effects. The first explored the possibility of using the liquid-solid technique to minimize the influence of pH variation on the release of loratadine. Several liquid solid formulations were prepared using propylene glycol as a liquid vehicle, MCC as a carrier, and silica as a coating material. The dissolution profile of the prepared liquid solid tablets was investigated in three buffered media with pH values of 1.2, 2.5, and 5, respectively. The results indicated that the dissolution rates of liquid-solid tablets were significantly higher and less affected by pH variation in comparison with the directly compressed tablets and marketed tablets [24].

Used as a promising tool to improve drug photostability in solid dosage form: A loss of drug potency during the photodegradation process may result in toxic degradation products and cause potential side effects, thus the photostability study is an indispensable part of pre-formulation studies for photosensitive drugs. The principle behind the photoprotective action of the liquid-solid technique is based on the photoprotective property of silicon dioxide (a commonly used coating material in liquid-solid systems) due to its high refractive index and the capability to diffract light waves of different energies. They designed a study to evaluate the possibility of using the liquid-solid technique as a promising alternative to conventional coating for the improvement of drug photostability. Several liquid solid formulations of amlodipine (a photosensitive drug) were prepared, where Avicel® PH 102 was used as the carrier, and nanometre-sized amorphous silicon and titanium dioxide either alone or in combination were used as the coating material. The prepared amlodipine liquid formulations were irradiated with visible light, UVA, and UVB with different light doses for eight hours [25].

RESULTS AND DISCUSSION

Pre Formulation Studies

The flow properties of the liquid-solid system are determined by the angle of repose, carr's index, and Hausner's ratio. The angle of repose was measured by the funnel and free-standing cone method. The bulk density and tapped density were determined for the calculation of Hausner's ratio and Carr's index (Table 4).

Table 4 Preformulations studies

Liquid Solid System	Angle of Repose	Carr's Index	Hausner's Ratio	Tapped Density	Bulk Density
Ls 1	26.35 ± 0.25	14.72 ± 0.21	1.14 ± 0.03	0.29 ± 0.02	0.22 ± 0.04
Ls 2	26.65 ± 0.20	15.30 ± 0.15	1.15 ± 0.04	0.28 ± 0.05	0.24 ± 0.02
Ls 3	27.01 ± 0.23	16.13 ± 0.32	1.19 ± 0.01	0.27 ± 0.15	0.23 ± 0.01
Ls 4	28.20 ± 0.45	17.82 ± 0.12	1.20 ± 0.03	0.32 ± 0.03	0.28 ± 0.02
Ls 5	31.50 ± 0.032	18.05 ± 0.53	1.22 ± 0.06	0.31 ± 0.01	0.27 ± 0.03
Ls 6	32.82 ± 0.55	19.02 ± 0.14	1.23 ± 0.04	0.33 ± 0.08	0.25 ± 0.01
Ls 7	33.86 ± 0.24	19.65 ± 0.44	1.18 ± 0.06	0.31 ± 0.04	0.27 ± 0.04
Ls 8	34.01 ± 0.01	20.24 ± 0.12	1.26 ± 0.07	0.34 ± 0.01	0.29 ± 0.02
Ls 9	28.56 ± 0.024	21.76 ± 0.94	1.28 ± 0.01	0.38 ± 0.02	0.27 ± 0.06

Particle Size Analysis of Phenytoin Tablet

The Phenytoin tablet percentage retained was found to be approximately 120 µ-170 µ. Particles in the size range have no serious problems like charge development. Therefore, it was decided to use the phenytoin as it can be used without any further processing like decreasing the particle size or adsorption or removal to decrease the cohesive force (Table 5).

Table 5 Phenytoin tablets with 120 µm-170 µm particles can be used directly without further processing

Sieve Number	Microns (µ)	Weight of Sieve	Final Weight	% retained	Cumulative% Weight Retained
20	75	349.8	355.6	5.63	99.5
30	90	350.5	357.8	6.64	93.9
40	125	354.5	375.6	20.43	87.3
60	150	358.6	382.6	21.49	66.9
80	212	361.2	372.6	20.37	45.5
100	200	364.7	393.4	25.26	25.2

Solubility Studies

The drug Phenytoin was determined to be slightly soluble and very slightly soluble to increase the solubility we added sodium lauryl sulphate as a surfactant. The solubility was found to be 0.3 mg/ml [26-34] (Figure 3 and Table 6).

Table 6 Solubility studies

Concentration	Absorbance
0	0
0.1	0.177
0.2	0.34
0.3	0.499
0.4	0.655
0.5	0.82

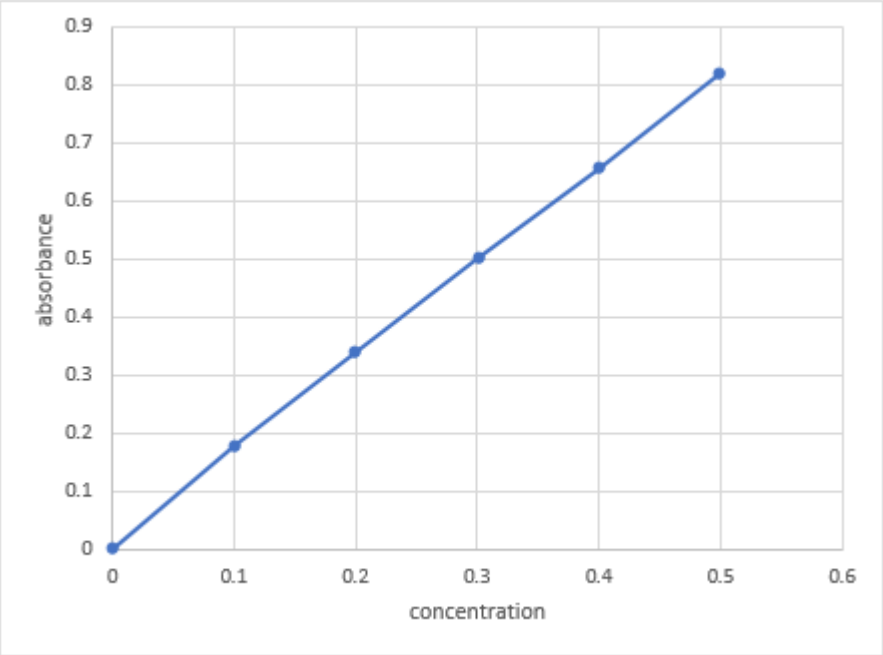

Figure 3 Concentration and absorbance

CONCLUSION

The liquid-solid technique was found to be a promising approach for improving the dissolution of a poorly soluble drug like phenytoin liquid solid tablets formulated with the propylene glycol at a drug concentration of 10% w/w is the best formulation among all the batches of liquid-solid tablets prepared, in terms of faster disintegration time, superior dissolution profile, and acceptable tablet properties. Propylene glycol was found to be a promising liquid vehicle in formulating liquid solid formulations of phenytoin the liquid vehicle plays a contributing role in improving the discussion profiles of a poorly water-soluble drug in the liquid solid formulations, besides choosing a suitable liquid vehicle according to its viscosity and HLB value. The key step in formulating a successful liquid-solid is the determination of the optimal flow able liquid retention potential.

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