

## **A Novel Formulations For Solubility Enhancement Of Sparingly Water-Soluble Drug Using Solvent Evaporation Method**

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**Abstract:** Phenylbutazone is a non-steroidal anti-inflammatory drug (NSAID) characterized by poorly water solubility, which influences negatively on the bioavailability. This research aims to improve the solubility of phenylbutazone by incorporating with two different types of silica at various surface area and pore size. It will also explore the effect of different ratios of silica on dissolution profiles. Phenylbutazone formulated with silicas were prepared using a solvent evaporating method, and the impregnated carriers characterized using XRD, Digital Microscopy, and particle size distribution analysis. There was a significant enhancement of drug release for all formulated products compared with the dissolution profile of pure drug. This enhancement can be ascribed to a large surface area of porous silica and improved wettability. Mesoporous silica SP 53D-11785 provided the highest drug release in comparison with silica gel, and this may be due to its capacity and also large internal pore volume, of silica SPD for greater loading with the drug because it has a highly accessible pore network.

**Keywords:** mesoporous silica, phenylbutazone, solvent evaporation, drug release.

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### **I. Introduction**

Recently, the pharmaceutical industry has expanded dramatically due to improvement in technological breakthroughs and combinatorial chemistry. All drugs contain active ingredients that are responsible for therapeutic effects. In addition, excipients are added to overcome particular issues, for example; to cover an unpleasant taste (flavouring agent); to increase the bulk of the drug (diluent) or to reduce cohesion and increase adhesion forces (lubricant agent and anti-adherence). Some excipients are used to modify drug release and also drug delivery: for example, compounds such as silica polymers and PAMAM dendrimers (Kisset al., 2006).

The two most important issues in drug manufacturing and discovery are adsorption and solubility, and one in ten marketed medicines have solubility problems and over one third of pipeline drugs are sparingly soluble. The solubility of drugs is classified into different types according to the biopharmaceutical classification system (BCS). Thus, they may be highly soluble and permeable, as in Class I. Alternatively, Class II drugs have low solubility and high permeability, while class III drugs have less affinity for permeation through cell membranes but high ability to dissolve when they cross the membrane. Meanwhile, drugs which have low solubility and permeability properties are classified as class IV (Liu & Che., 2015).

Drugs require a hydrophobic component to be capable of entering through cell membranes. However, they should also have the ability to dissolve inside cells from their hydrophilic properties (Limnell et al., 2011). Different methods have been reported to enhance the solubility of sparingly soluble drugs. For example, a change in the form of the active ingredient to a water soluble salt form, micronisation of drug particles, increasing of the wettability of the drug powder, adding a solubilising agent such as a surfactant, adding biocompatible drug carriers (liposomes, dendrimers) or formulation the drug inside the pores of silica (Yang et al., 2009). All of these methods have advantages and disadvantages. For instance, Yang et al. (2009) stated that there is a significant increase in the solubility of phenylbutazone using polyamidoamine (PAMAM) dendrimers. There are many benefits to using PAMAM dendrimers, firstly, they are more efficient than other carriers (cyclodextrins or micelles) due to their high density, secondly, they have a well-defined globular structure, size is controlled and thirdly they have a greater ability to penetrate cell membranes and are safer than protein carriers. However, the cytotoxicity of cationic dendrimers, combined with a short duration in blood and expensive prices are major disadvantages for using dendrimers as a drug carrier (Gu et al., 2013).

Ordered mesoporous silica is one approach which has drawn a great attention in improving the dissolution profile for sparingly soluble drugs. Kumar et al., (2014) stated that there was a significant difference in rate of dissolution and oral bioavailability between aceclofenac without silica and with different types of silica. Dissolution rate and solubility of carbamazepine were also enhanced by loading within mesoporous silica (Ali et al., 2013). Furosemide is used as a diuretic agent and is classified within class IV of the

Biopharmaceutics Classification System (BCS). Ambrogi et al. (2012) reported that by inclusion of furosemide in MCM-41 mesoporous, the dissolution rate and percentage of drug release were also improved. In addition, the rate of drug release of carvedilol was enhanced by impregnation of silica (Sylysia) with carvedilol (Planinsek et al., 2011). 2-benzyl- 5 – (4-chloro-phenyl)-6-{4- (methylthio) phenyl}-2H-pyridazin-3-one (K-832) is effective for the treatment of ischemic diseases, inflammatory conditions, and as a preventive due to the inhibition of the production of interleukin- 1B and cytokine. Miura et al. (2011) state that the solubility and absorption of K-832 were enhanced by using porous silica Sylysia 350 as a carrier. Enhancement of the dissolution rate, and decrease in gastric damage was also achieved by using 3DOM silica as a matrix for indomethacin nanoparticles (Hu et al., 2011). Ordered mesoporous silicate SBA-15 has been utilised to improve the dissolution profile for carbamazepine, cinnarizine, danazol, diazepam, fenofibrate, griseofulvin, indomethacin, ketoconazole, nifedipine and phenylbutazone (Van Speybroeck et al., 2009). Solubility and bioavailability of telmisartan were enhanced by loading inside the pores of mesoporous silica nanoparticles (MSNs) (Zhang et al., 2010). Sporanox is a trade name for itraconazole, which has antifungal activity and low solubility. Mellaerts et al. (2007) reported that an *in vitro* study confirmed an enhancement in the release of the hydrophobic drug itraconazole by impregnation of the drug with ordered mesoporous SBA-15 silica.

The aim of this work is to improve the solubility of phenylbutazone by formulating it with different types of silica at different ratios and evaluate the results of subsequent dissolution profiles.

## II. Materials and methods

### 1.1 Materials

Phenylbutazone ( $C_{19}H_{20}N_2O_2$ ) as an active drug was obtained from Sigma-Aldrich while dipotassium hydrogen phosphate ( $K_2HPO_4$ ) with purity 98 % and potassium dihydrogen phosphate ( $KH_2PO_4$ ) with purity 99 % were supplied by Fisher Scientific. Silica gel with pore size 60A , 70-230 mesh and 63-200  $\mu m$  was supplied by Sigma-Aldrich. SP53D-11785 with a particle size of approximately 3  $\mu m$ , surface area of 262  $m^2 g^{-1}$ , and pore volume of 1 cc/g and pore diameter of 150  $\text{\AA}$  was kindly donated by Glantreo, Ireland. Ethanol was purchased from Sigma Adrich (Dorset, UK) with minimum purity of 99 %. The material was utilized as received.

**Table 1:** A Summary of the physicochemical properties of the twodifferent types of silica used in this investigation.

Silica name	Surface area ( $m^2 g^{-1}$ )	Particle size ( $\mu m$ )	Pore volume (ml/g)	Manufacturer
Silica gel (SG)	500 $m^2 g^{-1}$	35 – 75 $\mu m$	0.75	Aldrich Chemistry
SP 53D-11785	262 $m^2 g^{-1}$	3 $\mu m$	1.00	Glantreo, Ireland

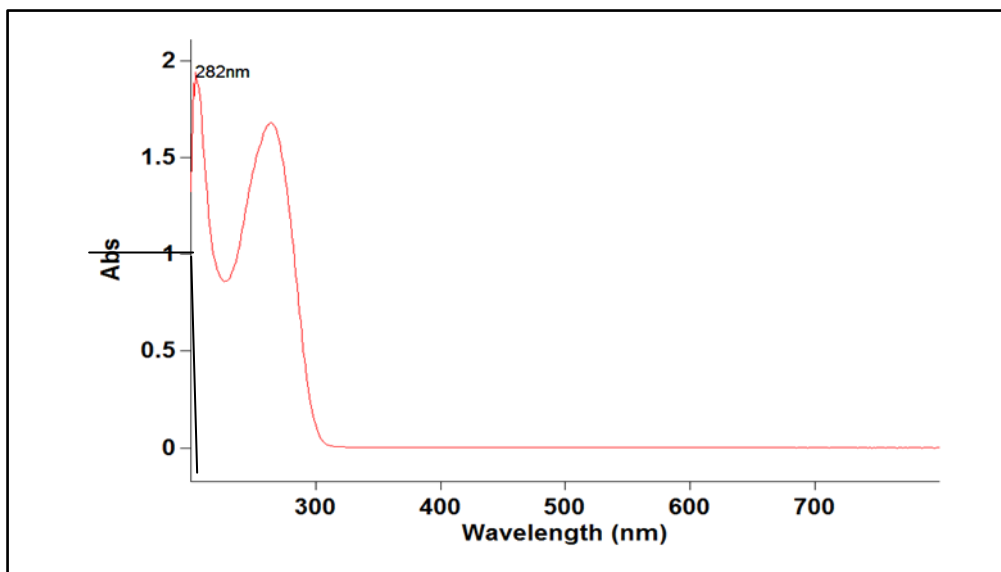
### 1.2 Methods

#### 2.2.1 Phosphate buffer

8.505 g of potassium dihydrogen phosphate ( $KH_2PO_4$ ) and 6.533 g of dipotassium hydrogen phosphate ( $K_2HPO_4$ ) were accurately weighed with an analytical balance (Mettler AT201) and transferred in to a 1000 ml volumetric flask, the solution were made up to the mark with deionised water, and pH analyser (Jenway 3510) was used to measure the pH of the solution after shaking the solution for 5min.

#### 2.2.2 Wavelength determination ( $\lambda_{max}$ )

A stock solution of 100  $\mu g ml^{-1}$  of phenylbutazone was prepared in phosphate buffer (pH 6.94) to determine the lambda max, the solution was sonicated (VWR-USC 300T) for 1 hour. Subsequently, a standard solution of 25  $\mu g ml^{-1}$  was prepared in a 25 ml volumetric flask, and a Cary 60 UV/Vis spectrophotometer was used to determine the wavelength of maximum absorption in the range 200 – 800 nm. Figure 6 shows the spectrum of phenylbutazone.



**Fig. 1.** Full scan of phenylbutazone using an Agilent (Carry 60) UV- Spectrophotometer.

### 2.2.3 Solvent evaporation method

Samples of two silica (silica gel, and SP 53D 11785) were each prepared with phenylbutazone at 1:1, 1:3 and 1:5 excipient/drug mass ratios using solvent evaporation technique. A sample mass (250 mg) of the drug was dissolved in 10 ml absolute ethanol and wetting of the different types of silica was continued in a beaker. The impregnation was placed on a hot plate stirrer with temperature gradually increased from 20 °C to 90 °C, monitored using a temperature probe. This temperature was maintained, while the solvent was evaporated in an air stream with the resultant product collected and dried at 37 °C overnight in a standard oven and passed through a 60 mesh screen to avoid agglomeration.

### 2.2.4 Characterization methods

Crystallinity of the samples were analysed using X-ray powder diffraction (XRD), a D<sub>2</sub>-Phaser (Bruker) X-ray diffractometer, equipped with a Cu K<sub>α1</sub> radiation source at 30 kV voltage, 10 mA current and 5 min scan speed. Diffraction patterns were obtained in the 2θ range of 5-50° using a 0.02 step size. The morphology of pure phenylbutazone and with different types and ratios of silica were performed with Keyence microscope (VHX-2000) equipped with microscope real zoom lens (RZ x200- x2500). The magnification range was between 200 - 2500 and samples 2 - 4 mg of each powder was put on the microscope slides (1mm thickness, 76 x 26mm dimensions) with cut, ground edge and without frosted marking area, the images were obtained on 3D display. The particle size distribution analysis (PSD) of the formulated powders were determined using Malvern Mastersizer 2000 (Malvern instrument limited, Worcestershire, UK) connected to a small volume sample dispersion unit which was filled with 100 - 150 ml deionised water (dispersant), 5 - 10 mg of all powders were each added in to the dispersion unit followed by adding 1 drop of surfactant (IGEPAL CA-630). Three replicates of each powder were measured, analysed and average obtained using Mastersizer 2000 software (version 5.61).

### 2.2.5 *In vitro* phenylbutazone release

Dissolution tests were carried out using Hanson research SR8-Plus dissolution apparatus. A (USP 2) paddle method was utilised at a rotational speed of 75.0 rpm and temperature of 37.0 ± 0.5 °C by using a thermostat bath. The dissolution vessels contained 900 ml of phosphate buffer (pH 6.94). The vessels with the buffer were sonicated for 10 min to get rid of the air bubbles. Samples with total drug contents of 22.5 mg were placed in the vessels containing 900 ml buffer. Aliquots of 4 ml were withdrawn from each of the 3 vessels at regular intervals from 5 min for 60 min and the absorbance was measured using Carry 60 UV/Vis spectrophotometer. Measurements were made in triplicates on pure phenylbutazone and phenylbutazone-loaded silica. Concentrations in the liquid samples were analysed using the equation of the graph and the mean of percentage drug release and their corresponding standard deviations were calculated.

## III. Results and discussion

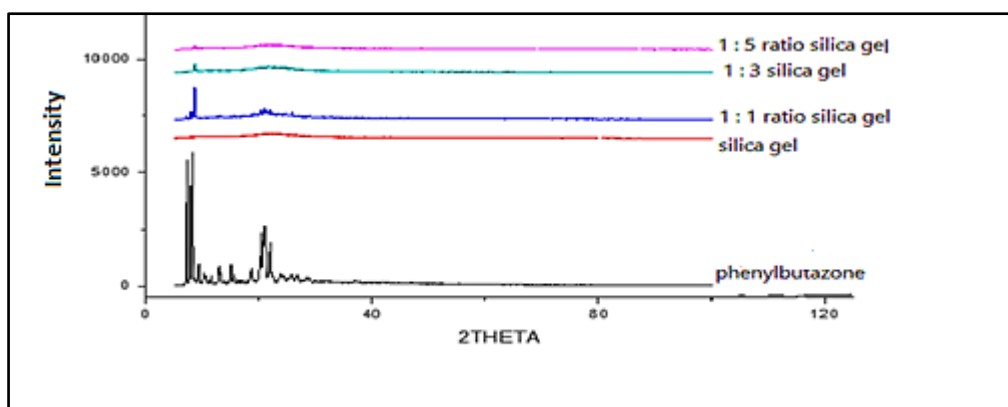
### 3.1. Characterization of formulations

The XRD pattern for the pure phenylbutazone shows sharp peak expected for a crystalline solid in comparison to the featureless pattern for the silica due to its amorphous form. Some minor XRD peaks due to

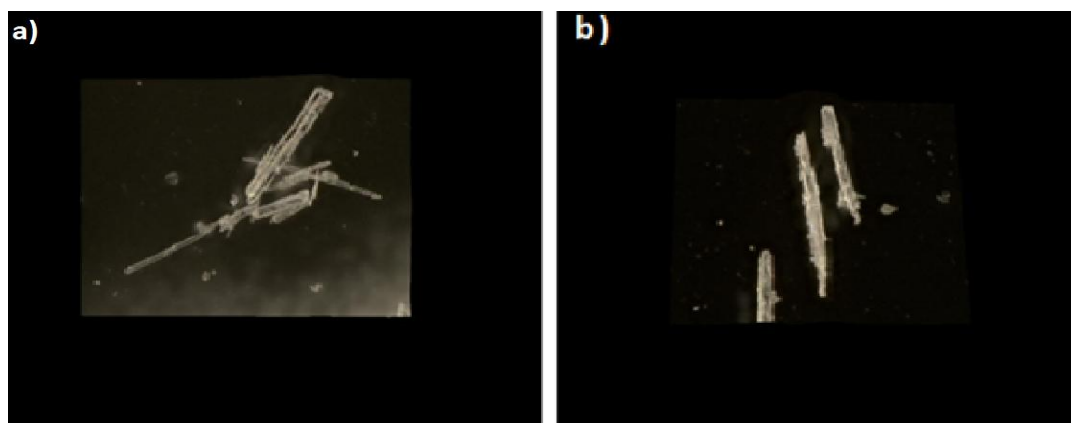
nanocrystals could be observe for phenylbutazone-silica gel based formulation and the percentage of crystalline form of phenylbutazone was decreased by incorporating it with different types of silica. Niu et al., (2013) stated that when there are no distinctive peaks for drug after incorporating it with mesoporous silica, it can be deduce that the drug is absorbed in the pores and on the surface of mesoporous silica as shown in Fig.2.

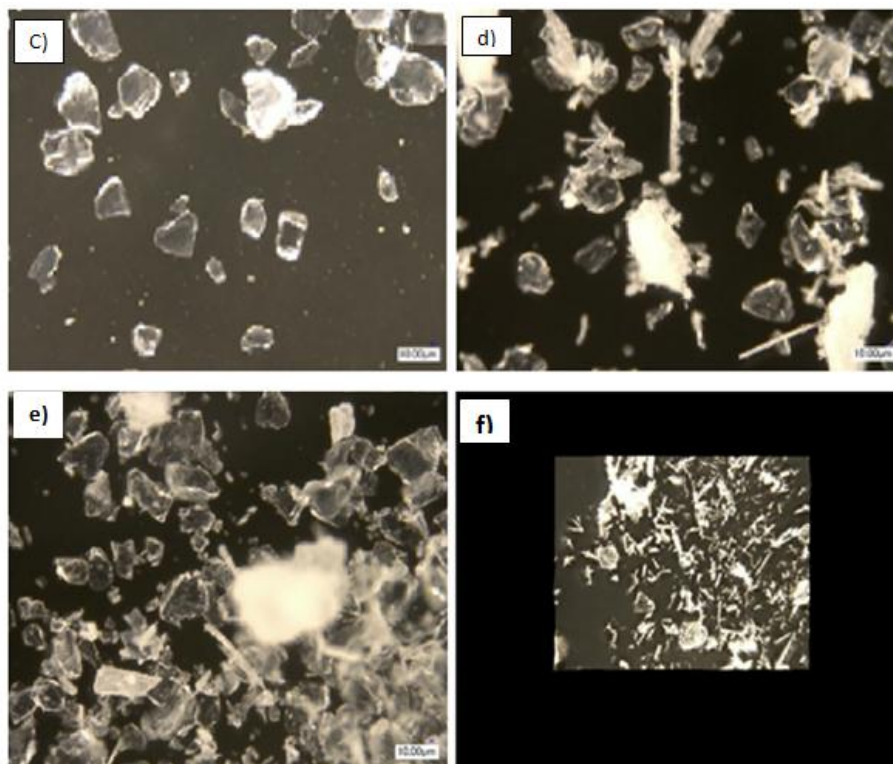
Digital microscopy images were utilised to indicate any observable differences in the physical characteristics of the formulated products compared with the pure phrnylbutazone or a solvent mixture of drug and silica. It can be seen from the images (fig. 3) that phenylbutazone has a needle-like shape and is crystalline in form while the silica has an amorphous shape. The high concentration of silica in high ratio samples shows the same morphology of pure silica. Furthermore, SP 53D-11785has a large surface area which illustrates the ability of it to provide more drug release than silica gel.

The particle size distribution analysis was determined with a laser light scattering method. Drug formulation with silica gel as illustrated in fig. 4, the size distribution is narrow from 5µm up to 1000 µm. Horcajada et al., 2004;Choudhari et al., 2014, reported that “the peak with narrow particle size distribution supports a defined adsorption/desorption profile with more kinetics compared to an adsorbent with wider particle size distribution”. Span indicates for the width of distribution and it’s the distance between two points equally spaced from the medina (Wolfrom, 2011). However, particle size distribution is not an effective indication because phenylbutazone is a strongly cohesive powder.

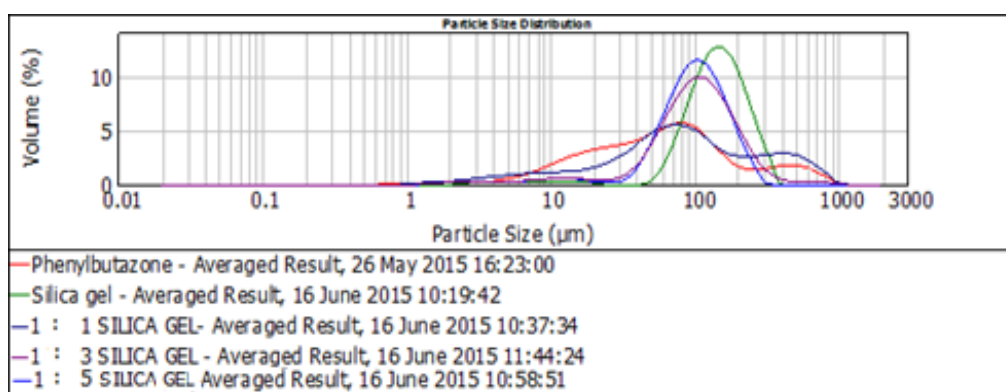


**Fig. 2.** XRD scan of pure phenylbutazone and phenylbutazone loaded silica gel with three ratios (1:1, 1:3, and 1:5).

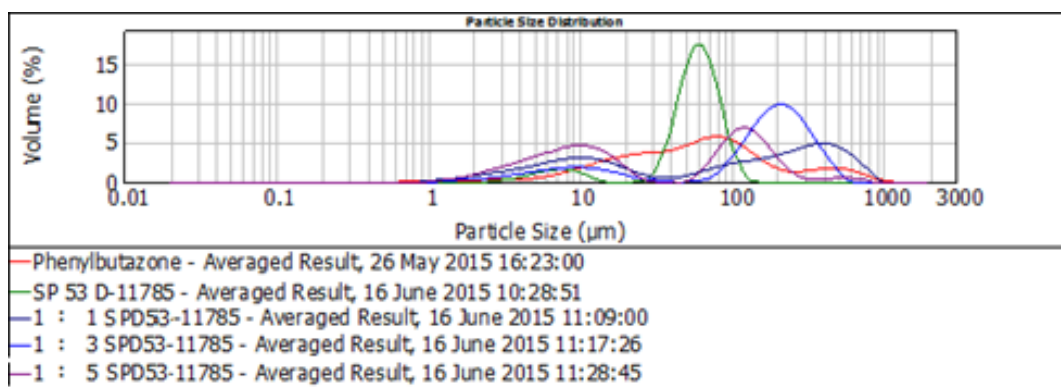




**Fig.1.** Digital microscopy images (KEYENCE VH- Z 250R) with lens RZ x250 - x2500, a shows the pure silica gel. While 1:1 ratio, 1:3 and 1:5 ratio were illustrated in pictures b, c, and d respectively.



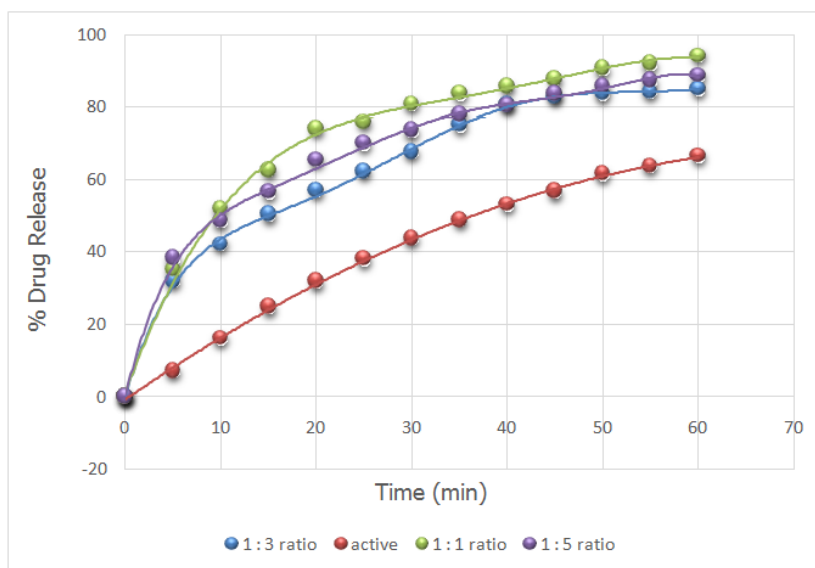
**Fig.4.** Particle size distribution of phenylbutazone and silica gel with three different ratios (1:1, 1:3 and 1:5 ratios)



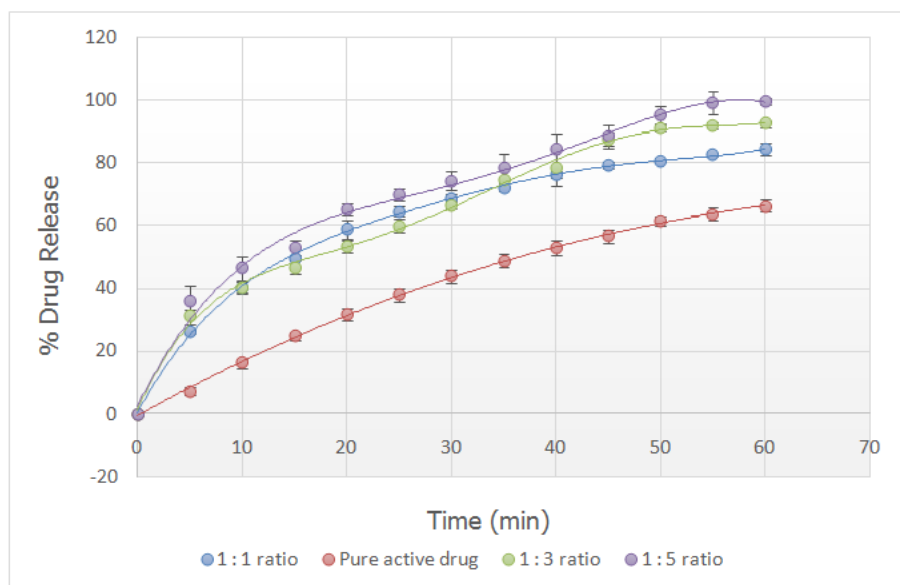
**Fig.5.** Particle size distribution of phenylbutazone and SP 53 D-11785 with three different ratios (1:1, 1:3 and 1:5 ratios).

### 3.2 In vitro dissolution analysis

Drug release for 9 formulations was measured using standard dissolution analysis apparatus over a period of 60 minutes, as demonstrated with silica gel in Fig. 6, and SP 53D-11785 in Fig. 8. Generally, there was a significant enhancement in the dissolution profile of phenylbutazone after formulating it with different types and ratios of silica. By comparing the percentage of release of pure drug and drug silica-silica gel formulation, and SP 53D-11785 for 1: 1 ratio after 5 minutes, the percentages of drug release were  $7.2 \pm 1.4 \%$ ,  $34.8 \pm 1.2 \%$ , and  $26.1 \pm 1.1 \%$  respectively. Such a significant enhancement in drug release was ascribed to finite-size effects which means the ability of silica to save the drug molecules in amorphous form and prevent to retain to the crystalline state, with ultimately a large surface area of porous silica and improved wettability (Alba-Simionescu et al., 2006). It can be seen that more silica equals more drug release for all types of silica except for silica gel. Regarding silica gel, 1:1 product provided the greatest release ( $90.9 \pm 3.4 \%$ ) after 60 minutes, whereas for 1:3 and 1:5 this were  $85.3 \pm 1.3 \%$  and  $88.5 \pm 3.7 \%$  respectively.



**Fig.6.**Phenylbutazone release profiles for phenylbutazone along with silica gel based formulations using the solvent evaporating method, all at drug/silica ratios of 1:1, 1: 3, and 1: 5. Each data point represents the mean of 3 results with SD error bars.



**Fig.7.**Phenylbutazone release profiles for phenylbutazone along with SP 53D-11785 based formulation using the solvent evaporating method, all at drug/silica ratios of 1:1, 1: 3, and 1: 5. Each data point represents the mean of 3 results with SD error bars.

The higher percentage drug release for the 1:1 ratio may be due to a small pore volume of silica gel (0.75 mg/ml) compared to that of SP 53D-11785, and as a result the drug release was slow due to steric hindrance blocking the diffusion of particles of the drug outside the porous. Therefore, when a large mass of drug was added, this provides more chance of the drug being incorporated in the pore and adsorbed on the surface of the silica. Consequently, the percentage of drug release was increased (Qu et al., 2006). By comparing the percentage of drug release for phenylbutazone with SP 53D-11785, a 1: 5 product of SP53D-11785 provided the highest extent of drug release ( $99.5 \pm 1.1$  %) after 60 minutes. This can be explained by the large concentration of silica in this ratio, which led to more surface area and large internal pore volume. This enhancement can be explained by these factors: firstly, the large internal pore volume, unique morphology and the capacity of SP 53D 11785 to allow more loading of the drug because it has a highly accessible pore network. In addition, SP 53D 11785 act as an anti-static agent that help to reduce the cohesive force of phenylbutazone (Grace Davison Discovery Sciences). It can be seen that the most important parameter to obtain high load efficiency was the pore volume as in loading of indomethacin with SBA-15 and MCM-41 (Mellaerts et al., 2008). However, there was no considerable effect of particle size on drug loading as when incorporating ibuprofen with mesoporous silica (Shen et al., 2011)

#### IV. Conclusions

The aim of this research was to evaluate the effect of different mesoporous silica on the dissolution behaviour of hydrophobic drug (phenylbutazone). Four objective were evaluated to reach the research aim. In this research, a standard solution of phenylbutazone was prepared in order to calculate the unknown concentration of phenylbutazone. Phenylbutazone was incorporated inside different types and ratios using the solvent evaporating technique. The dissolution profile and percentage of drug release of pure phenylbutazone and after incorporation with two types of silica (silica gel, and SP 53D-11785) with three ratios (1:1, 1:3 and 1:5) were calculated and compared. Light microscopy, XRD and a particle size counter (Mastersizer 2000 rpm) were used to investigate the effect of silica on the drug. The performance of different types and various ratios of mesoporous silica as a carrier for the sparingly water soluble drug phenylbutazone has been investigated using *in vitro* study. Silica based formulations provided a faster dissolution rate when compared to pure phenylbutazone. From this study, it can be deduced that using mesoporous silica assisted in improving the dissolution rate of this sparingly soluble drug and there was no great effect of particle size on drug release. However, greater pore volume capacity provided a significant effect on the drug release because it has more loading capacity. The objective of this research were effectively accomplished. Consequently, the aim of this project was achieved. However, characterisation methods were not a great indication to explore the effect and loaded of silica.

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