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Guar gum based matrix tablets for modified release

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ABSTRACT

Extended-release model allows at least a twofold decrease in the drug dose frequency compared to the conventional (immediate release) dosage form. The current study investigates the guar gum modified release tablet containing glycine and guar gum with different ratios and investigate the modified release tablets containing polyvinyl-pyrrolidone (PVP) by wet granulation method. The tablets were tested according to the British Pharmacopeia (BP) with the appropriate tests. The relation of the swelling factor to the concentration of guar gum and glycine depended on the ratios used such that decrease in glycine or increase in guar gum increased the swelling factor. The formulations having low amounts of glycine and high amounts of guar gum mainly depend on the high swelling index of guar gum. High glycine and low guar gum ratios enhance the matrix erosion in direct proportion manner. This proved that the higher swelling and the lower erosion could be obtained by reducing the glycine and increasing the guar gum to form stronger gel for the design extended release formulations. Moreover, the hydrophilic property of the PVP enhances dramatically the swelling index of the matrix with an unclear increase in the erosion. The PVP increases the swelling of the matrix of formulation 2 from 297.6% to 342.7% and the erosion from 39.1% to 40.6%. The (5 % glycine and 55 % guar gum) formulation was the best formulation out of the glycine and guar gum blends for the sustained release purposes as it described the slowest release out of the guar gum and glycine formulations which enabled the table to be administered every 16 hours. Additionally, on adding polyvinyl-pyrrolidone (PVP), it enabled the release of the theophylline dose over 20hours, which could lead to one-day administration of the theophylline tablet. According to the aforementioned results, the formulation including the glycine, guar gum and PVP blends was found to be the best model for the extended-release tablets.

Keywords— *Guar gum, Glycine, Polyvinylpyrolidone, Theophylline, Direct compression, Wet granulation*

1. INTRODUCTION

The hydrophilic matrix tablet system has proven to be one of the most used techniques for oral controlled drug delivery system because it Is characterized by having a good drug release profile and has a low-cost production. Hydrophilic matrix tablets systems are mostly being used for extended release of drugs. One of their many advantages is that they utilise standard, but safe excipients, utilize also advanced technologies and can enclose huge drug amounts, then a water-swellable, hydrophilic polymer is blended with the drug and then the moment its exposed to any solution, the polymer material will swell and transform into a hydrated gel matrix, this gel can hinder the release of the dissolved drug enclosed [1]. In order for the drug to release for the gel, it must go through some complex interactions of diffusion, erosion and swelling of the polymer. The drug release rate will also be greatly affected by the water diffusion rate through it [2]. The gel matrix consists of the cross-linked strands forming network between which space allows the water and drug diffusion. Increasing polymer concentration or molecular weight increases the gel viscosity, which in turn slows down the drug release rate [3].

1.1. Guar gum

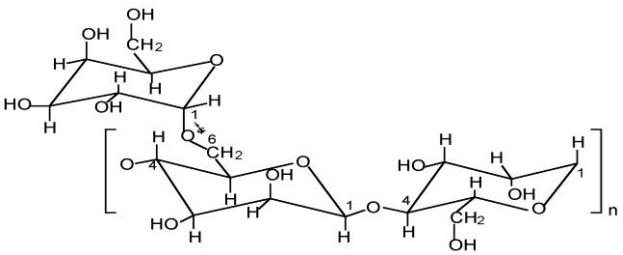

Fig. 1: Structure of guar gum

Thanks to its high molecular weight, which is up to (200,000-300,000 Daltons) beside the protracted repeating unit created by the bonding of hydrogen, guar gum can create greatly viscous, pseudoplastic hydrophilic solution regardless at low or high concentrations. This characteristic lets the solubility of guar gum and permits It to to be gel even in cold water [4,5]. The Chemical structure of guar gum has a linear series of β-(1→4)-linked D-mannos pyranose units connected to (1→6)-linked α-D-

galactopyranose remains as side series in the company of galactose: mannose ratio is roughly1: 2. It is not influenced by the different pH due to its non-ionic property and it is stable in pH ranges from 5 to 7 pH with expected degradation on excessive heat and too high pH [6,7].

Products with guar gum illustrate a distinct temperature thinning result once their solutions are exposed to heat. This is achieved by the loss of hydration water surround the molecule of polymers. Consequently, this action allows it to be the most appropriate natural polymer [7]. Guar gum is utilised as a binder in tablets in order to make the powder of drug more cohesive. It is also utilised as an agent for controlled release drug owing to the great rate of hydration (swelling in aqueous media) [8].

Moreover, it is utilised in the different pharmaceutical formulations to improve and adjust the stability and thickness of the products. With adding it to different constituents in the tablets formulation, it creates a protective film. Therefore, the release of the drug where the guar gum inside in the tablets is expected to be a sustained mode, accomplishing the required kinetic effect beside to its function in masking the unpleasant flavour and odour of drugs [9]. Y.S.R.Krishnaiah et al produced 3-layer matrix tablets of trimetazidine dihydrochloride. After the evaluation of the thickness, hardness, uniformity of drug content and dissolution testing of the tablets, the results obviously showed that the function of guar gum in the design of a 3-layer matrix system was a good hydrophilic carrier in the form of oral controlled release drug systems, especially for greatly soluble drugs [10, 11].

RishabhaMalviyaet al worked to develop sustained release matrix tablets using diclofenac sodium as a drug and guar gum to modify the release. That was done after the evaluation of the thickness, hardness, uniformity of drug content and dissolution testing of the tablets was carried out in phosphate buffer saline at pH 7.4 for 24 hours. The results illustrated that the release profile of the drug from matrix tablets performed utilising guar gum delayed approximately 24 hours. Therefore, guar gum is considered an excellent applicant for 80 sustained release formulations [12].

1.2. Glycine

Glycine is considered the smallest amino acid in nature and its chemical formula is NH_2-CH_2-COOH. It has many pharmaceutical applications such as buffering agent, lyophilized products stabilizer and various pharmaceutical solutions.

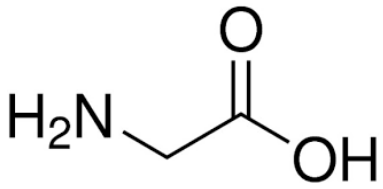

Fig. 2: Structure of glycine

Glycine acts as zwitterions due to the proton transfer from the carboxylic group to the amino group. The zwitterions form of the glycine can interact with guar gum to modify the physicochemical properties such as viscosity, swelling index, erosion rate and gel formation to control the drug disillusion and release over long periods of time according to the ratios of the gum and glycine [13].

In the current project, glycine will be used with guar gum in six formulations by direct compression method and with PVP plus guar gum in one formulation designed by wet granulation method to extend the release profile of theophylline from the guar gum matrices. The degree of interaction between the glycine and guar gum will be affected by their ratios to manipulate the swelling factor of the formulation, which finally controls the release of the drug.

1.3 Theophylline

According to its structure, the classification of theophylline is methylxanthine. It is characterised as a white crystalline powder with an astringent taste with no odour. The chemical name of anhydrous theophylline is 1H-Purine-2,6-dione, 3,7-dihydro-1,3-dimethyl and its molecular formula is $C_7H_8N_4O_2$.

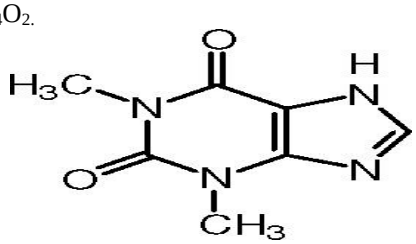

Fig. 3: Structure of theophylline

Due to its bronchodilator properties, theophylline is used for treating the symptoms and reversible airflow obstruction combine with chronic asthma and other chronic bronchi diseases, such as emphysema and chronic bronchitis. As a consequence of its low therapeutic index, theophylline is appropriate to be used in a matrix tablet. That means the release from the tablets should be cautiously controlled to avoid releasing a large quantity of theophylline, which could be toxic. [14].

1.4. Silicified Microcrystalline Cellulose (SMCC)

SMCC contains 98% of microcrystalline cellulose (MCC) plus 2% of colloidal silicon dioxide. The microcrystalline cellulose Silicification is accomplished through a process, causing an intimate relationship between both the microcrystalline cellulose and

colloidal silicon dioxide. SMCC associates the superb compact properties of microcrystalline cellulose with greater flow characteristics. Consequently, it is perfectly suitable for formulations, particularly in direct compression due to its significant advantages in both compatibility and the flow Compactibility forward the wet granulation is maintained [15].

Moreover, it shows brittle breakage and plastic perversion properties,achieving excellent binding characteristics. Furthermore, it needs lower pressure for compression with higher lubrication efficiency. In addition, the material gives enhanced resistance to the degrading influences of magnesium stearate versus the regular microcrystalline cellulose. In this project, SMCC 90 was used over SMCC 50 since it improves both flowability and compaction, while SMCC 50 provides the compaction only.

1.5. Magnesium stearate

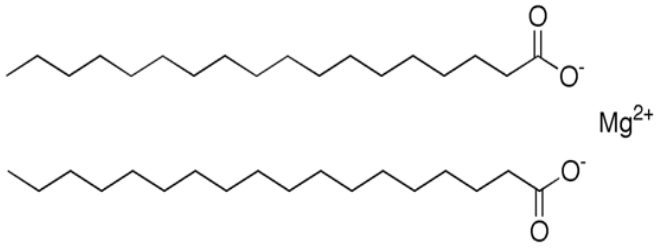

Fig. 4: The structure of magnesium stearate

Magnesium stearate is a very fine, white snowy powder with a dim odour of stearic acid and a characteristic flavour. It essentially consists of different percentages of both magnesium stearate plus magnesium palmitate.

It is mainly utilised as a lubricant in tablet manufacturing and works to rises the time it takes for tablets to be dissolved since it forms a film on the tablet constituents. Magnesium stearate has many advantages where the excellent required flow can be accomplished and low ejection pressure required [16].

1.6. Polyvinyl-Pyrrolidone (PVP)

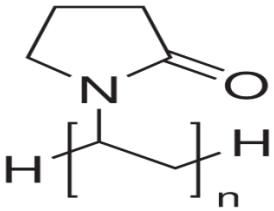

Fig. 5: The structure of polyvinyl-pyrrolidone

Synthetic polymers are utilized in pharmaceutical applications for several decades. It includes hydrophilic polymers like Polyvinyl-Pyrrolidone(PVP), which are hydro gel-forming polymers to control the release of the drugs by swelling,cross-linking and release of the entrapped drug. The hydrophilic sustained release matrix tablets are simple, economic and reduce the risk of toxicity due to the dose dumping through water penetration, polymer swelling, dissolving the drug that diffuses through the gels and polymer erosion. The polymer composition, molecular weight, amount, viscosity and modulation in the matrix system can control the plasma drug profile over the period [17].

1.7. Dry Granulation, Wet Granulation and Direct Compression Tableting

There are three different methods can be utilised to prepare the mixture prior to the stage of compression: direct compression, dry granulation, or wet granulation.

Firstly, direct compression is applied for powders that can be completely mixed and do not need more previous granulation steps to be ready for the process of tablet compression [18].

Secondly, dry granulation where the process steps of mixing the all ingredients before compaction and reducing the particle size of the mixture in furtherance of producing a granular and a free flowing mixture of identical size. For the sake of producing uniform and qualified compressed tablets, it is necessary that the mixture of ingredients represented to the compression step be dry and with identical particle size. Moreover, it is essential that the Active Pharmaceutical Ingredient (API)be distributed well inside each single produced tablet. If this is difficult to be achieved simply with sufficient mixing, the ingredients should undergo a further step for the granulation before the compression step of the press . That is in order to achieve a certain distribution of the active pharmaceutical ingredient within the final produced tablet [19].

Thirdly, the wet granulation method where the granules are produced by adding liquid binders to the powder blend. However, continuous mixing for the dry granulation and Continuous Direct Compression (CDC) operations include the single loading and precise applying of the Active Pharmaceutical Ingredients (API) and different excipients to a continuous mixer [20].

2. AIM AND OBJECTIVES

This project was aim to conduct some different trials in order to perform extended-release theophylline tablets in various formulations with different proportion of guar gum and glycine with adding polyvinyl-pyrrolidone as a liquid binder in one

formulation in expectantly to provide the performance of release for all tablets depending on the interaction of the guar gum with glycine and the effect of polyvinyl-pyrolidone in case of the wet formulation [21].

3. METHODS AND MATERIALS

3.1. Materials

For the preparation of tablets, there were many different materials used such as the guar gum, the talc and the glycine, which were ordered from (Sigma-Aldrich). Moreover, the SMCC 90 was provided by (Penwestpharmaceuticals)and the theophylline was supplied by (BASF chemicals). In addition, the magnesium stearate was brought from (BDH Chemicals). Furthermore, the polyvinyl-pyrrolidone(PVP) was ordered from (Sigma). Finally, the potassium dihydrogen and disodium hydrogen that were used in the preparation of the phosphate buffer solution was supplied by (Fisher Scientific).

3.2. Apparatuses

This project was carried out with using different equipment such as an electronic balance (Am 100, MettlerInstruments,Switzerland), a 4 digit balance (OHaus explorer, New Jersy,USA), a turbula mixer (Glen Creston, Stanmore, UK), a tableting machine (F3, Manesty machines, Liverpool, England), a UV spectroscopy (M501 single beam, spectroniccamspec, Leeds, England), a tablets hardness tester machine (2E, scheulinger, Switzerland), friability Machine (FR 1000, Copley scientific, Nottingham,England), an oven model (LEEC, Nottingham, England).In addition to some sieves with different size (1 mm,0.700 mm, 0.350 mm and 0.300 mm) were utilized.

3.3. Making of tablets

The tablets of the six formulations were made to the composition with different ratios of guar gum to glycine where formulation number 1 the ratio was (3:1), formulation 2 was (2:1), formulation 3 was (5:1), formulation 4 was (1:1), formulation 5 was (10:1) and formulation 6 was (1:2). Moreover, formulation 7 was with the same ratio as formulation 2 but in wet granulation form.

All ingredients were accurately weighed by utilising both the electronic balance (AM 100) and the 4-digit balance. The last type of balance was used especially for weighing the very small amount of materials, especially the talc and the magnesium stearate. After adding all the weighed materials together except the magnesium stearate, the combination for the formulation was mixed well by utilising a turbula mixer for 3 minutes at 45rpm. Then the magnesium stearate was added and the whole formulation was mixed together again for 1 minute at the same rotation speed and that was to provide the function of the magnesium stearate as a lubricant. According to the direct compression method, the whole combination was compressed automatically into uniform tablets by utilising a tabletting machine with constant force of 35kn and this force was the same with the six batches, while F7 was done by the previous method with some extra steps such as adding a binder solution of polyvinyl-pyrrolidone (PVP) to the ingredients and changing the force of the compression. In more details, the binder solution was prepared by replacing 4g of (PVP) in a 100 ml volumetric flask, then up it with distilled water, then the flask was left in a water bath for 60 minutes at 60°C to make sure the powder completely dissolved and then 30ml of 4% PVP solution was added to all the ingredients of F7 in (**table 1**) to make a wet mass. This wet mass was performed as granules by using a 1mm sieve, and then they were kept at room temperature until the next day to be completely dry. After that, these granules were filtered twice again by using two different sizes of sieves, 700µm and 300µm respectively. Finally, the final granulations were presented to the tabletting machine and were compressed at the force of 37kn.

Table 1: The composition of the seven formulations

Formulations	F1(g)	F2(g)	F3(g)	F4(g)	F5(g)	F6(g)	F7(g)
Guar gum	22	20	24	15	27	10	20
Glycine	8	10	6	15	3	20	10
Theophylline	11	11	11	11	11	11	11
SMCC	8	8	8	8	8	8	8
Magnesium stearate	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Talc	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Total weight	50	50	50	50	50	50	50

3.4. Preparation of the buffer solution

The five times concentrated buffer solution was prepared up by dissolving**63.559g** of potassium dihydrogen and **170.352** g of disodium hydrogen in 5 litres of distilled water. Then 1 litre of this concentrated buffer solution was added to more 4 litres of distilled water**.**

3.5. Calibration curve

The stock solution was prepared by adding 250 mg of theophylline in 500ml of the buffer solution (the phosphate buffer). A series of the stock solution was prepared at different concentration as the following 2.5µg/ml, 5µg/ml , 7.5µg/ml, 10µg/ml, 12.5µg/ml , 15µg/ml ,17.5µg/ml and 20µg/ml. Then every single concentration was made up in a 50ml volumetric flask and up it with phosphate buffer. The standard solutions were analysed by utilizing UV spectroscopy and the wavelength was adjusted at 270nm. The readings of the absorbance were measured three times to take the average for every single solution. Finally, a calibration grave was drawn, and then the equation was detected.

3.6. Evaluation of tablets

3.6.1. Uniformity of weight: The aim of this test to check if every single mass was in the limits, which has been identified by the British Pharmacopoeia (BP). The BP provides for "*Not more than two of the single masses deviate from the mean of mass by more than five percent and none deviate more ten percent*" (British pharmacopoeia, 2015).

This test was done by selecting 20 tablets randomly from every single formulation then they were weighed individually one by one utilising the four digital balance, then the average of the mass of every single formulation was calculated.

3.6.2. Tensile strengths, hardness and density of tablets: This test was carried out by choosing 10 tablets randomly of each formulation from the seven formulations and determining their diameter and thickness by utilising a micrometre. Every single tablet was placed into a tablets hardness tester machine then the crushing capacity was detected in KGF. The following Formula utilised to determine the tensile strength from the final results:

Equation 1: $TS=2F/\pi dh$
Where F is the force, π is constant equals to *3.14* and d stands for the diameter of the tablets and h refers to the thickness.
The density of tablets was determined using the following formulation:

Equation 2*D*: *The mass of tablets / the volume of tablets*

The volume of tablets was calculated by applying the following formulation:
Equation 3: $V=\pi r^2 h$
Where π is constant and equals to *3.14*, r^2 is the diameter of tablets and h is the thickness of the tablet.

3.6.3. Friability testing: The test of friability was carried out by choosing randomly 20 tablets from every single formulation and weighing them together before adding them to the friability Machine. The number of rotations was 100 times and the speed was 25rpm, then the 20 tablets were weighed once again to calculate the difference in weight before and after the test. The tablet passes this test according to the British Pharmacopeia text, which provides for "*the maximum loss of mass should not be more than 1.0 %"*

3.6.4. Uniformity of content: Three tablets were selected randomly from every single formulation to check the uniformity of content and they were weighted by using the four-digit balance, then each tablet was milled down by a moulder and placed in a 100ml volumetric flask to be dissolved in phosphate buffer then the solution in the flasks were sonicated for half an hour. Some solution of each flask was filtered to take 1mL of it to be diluted in a 50mL volumetric flask with the same buffer solution. The absorbance of the solution was investigated by utilising the UV spectroscopy where the wavelength was 270nm. According to the British pharmacopoeia to pass the test, every single content should be between 85% and 115% of the mean of content and the preparation cannot be passed in two cases. Firstly, if more than one single content deviates from these limits. Secondly, if one single content is not between75% and 125% of the mean of the content.

3.6.5. *In vitro* dissolution studies: This test was carried out by choosing three tablets from each formulation after weighing them. The temperature of the dissolution apparatus was adjusted at 37°C and the speed of the paddles was constant at 50rpm. After that, each vessel of the dissolution apparatus was full with 1 litre of phosphate buffer. Subsequently, each tablet was placed into its individual vessel. The test was performed over 8 hours with extracting 10mL of each sample and replaced with the same amount of the phosphate buffer which was at the same temperature over the 8 hours as the following: half an hour, one hour, two hours, three hours, four hours, five hours, six hours, seven hours and eight hours. The all withdrawn samples were analyzed by using the UV spectroscopy at a wavelength 270nm, and then the absorbance of each sample was recorded three times to take the average. The calibration graph was used to determine the concentration of the drug release by using the formula of the line (Figure 6). Subsequently, the concentrations were determined by a formula to remunerate for volume correction at various time points. The formula is as the following:

Equation 4: $Concentration\ 1 = C \times Vm$
*Where c is the concentration of the drug released and Vm is the volume of the media.

Equation 5: $More\ concentrations = C \times Vm + (Verb \times C1)$
Where vr is the volume replaced and $C1$ is the concentration determined from (equation 4).
This process was done for the rest of the tablets of every single formulation.

The following formula was used in order to determine the proportion release of the total drug:
Equation 6: *(Drug release/total drug) ×100*
When the test was done after 8 hours, the tablets were cautiously taken out the vessels. Each tablet was placed on the pre-weighed container, and then they were weighted by using the digital balance after making sure that any extra drops of water were uninvolved and the container was completely dry and clean [22]. This step was repeated for each tablet to determine the exact swelling percentage through the following formula:

Equation 7: $Swelling\ Index\ (\%) = \frac{W_s - W_i}{W_i} \times 100$
Where W_s represents the swollen sample while W_i represents the initial mass of the tablet.

All the tablets were kept in the oven where the temperature was around 70°C for the next day in order to dry them. The tablets with the container were weighted together again after making sure that they were completely dry without moisture in order to determine the erosion percentage by applying the following formula [23]
Equation 8: $Erosion\ Percent\ (\%) = \frac{W_i - W_t}{W_i} \times 100$
Where W_i is the initial mass of the tablet, whileWt is the mass of the dried tablet.

3.6.6 Kinetic modelling: The kinetics of drug release was calculated using the results of the dissolution test and after plotting the lines in different ways to perform the kinetics models for example zero order, first order, Higutchi, Korsmeyer-peppas, and finally Hixson-Crowell [24]. Zero order was achieved describing the drug dissolution of many kinds of modified release formulations. The following formula is used to obtain the results:

Equation 9: *Zero order =Qt + Q0 + k0t*
Where Qt represents the quantity of the dissolved drug, Q0 represents the initial quantity of drug within the dissolution medium, K0t represents the kinetics of zero order and t refers to the time. The chart is performed as the percentage of the released drug versus the time.

The first order was performed to assist in the description of the drug dissolution in formulations.

Equation 10: *First order = log Qt=log Q0+k1t*
Where *Qt* represents the quantity of the unreleased drug, *Q0* represents the initial quantity of the drug in the dissolution medium, K1is the kinetics of the first order with t, which represent the time. The chart is performed as the log percentage of the unreleased drug versus the time.

Higuchi model was applied to explain the dissolution of the drug comes out of a matrix tablet using the following formula:
Equation 11: *Higuchi = Qt= Kh x t1/2*
Where *Qt* represents the quantity of the dissolved drug in a specific time, *Kh* represents Higuchi dissolution constant while *t* represents the time. The chart is performed through the proportion of released drug versus the square root of time.

Korsmeyer-Peppas model was utilised to evaluate if the dosage forms follow either Fickiane diffusion or non-Fickiane diffusion using the following formula:
Equation 12: $Korsmeyer\text{-}Peppas=M_t/M_{\infty=kt}{}^n$
Where $Mt/M\infty$ represents the portion of the released drug at a specific time*(t)*, *k* refers to the rate of released content and represents the release exponent. The chart is performed by plotting the log time versus the proportion of released drug.

Finally, the model of Hixson-Crowell using the following formula**;**
Equation 13: Hixson-crowell= Q01/3 -Qt1/3 = Kst
Where *Q0* still as it is in the previous model, *Qt* refers to the quantity of the unreleased drug, while *Ks* represents Hixson-Crowell constant at a particular time (t).

4. RESULT AND DISCUSSION

4.1 Calibration curve

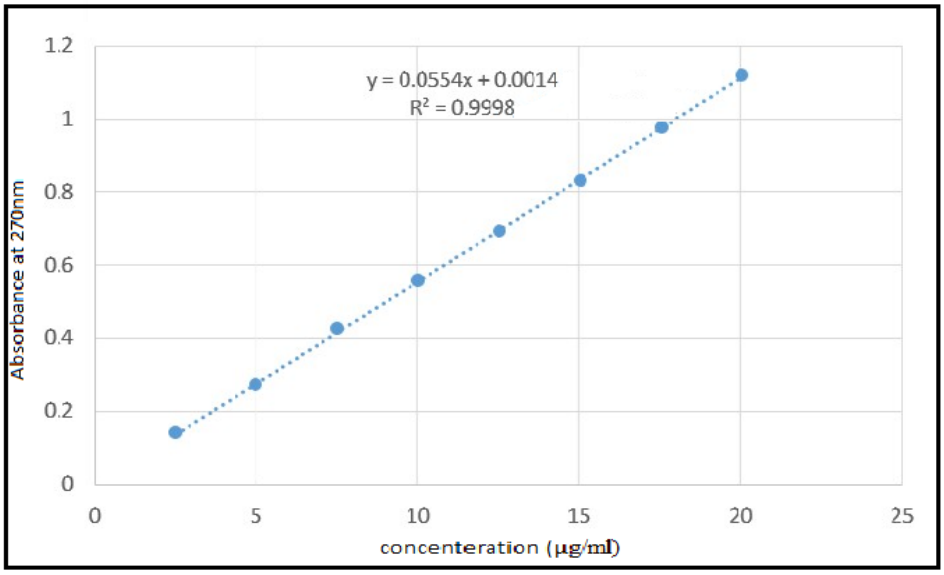

Fig. 6: Calibration for theophylline

It is necessary to detect the equation from the calibration curve for the results of the drug content test and the profile of drug dissolution. As it has been mentioned before in the method section the averages of the two absorbances of the standard concentrations were plotted to perform a calibration curve (Figure 6). Focusing on the graph, it is recognised that the linearity was good with the value of R^2 which was 0.9998. Moreover, the equation of the line was *y =0.0554 + 0.0014*.

4.2. Uniformity of weight

According to the British Pharmacopeia, which provides for "*Not more than two of the single masses deviate from the mean of mass by more than five percent and none deviate moreten percent*" (British pharmacopoeia 2015). The average of the mass of every single formulation was calculated after selecting 20 tablets randomly from every single formulation and after weighing them individually one by one utilising the four digital balance the results of all the tablets of the seven formulations were recorded (Table 2).

Table 2: Average masses of formulation

Formulation	F1	F2	F3	F4	F5	F6	F7
Average mass(mg)	308.71 ± 5.49	312.51 ± 1.67	307.84 ± 5.75	304.68 ± 4.05	311.03 ± 1.24	309.57 ± 5.12	307.57 ± 2.91

Focussing on the results after finishing this test, it is recognised that the tablets are all almost identical in the weight and no tablets differ from the average of weighing. This means that all formulations passed according to the standardisation of the British pharmacopoeia (2015).

4.3. Tensile strengths, hardness and density of tablets

The test was carried out by choosing 10 tablets randomly of each formulation out of the seven formulations after determining their diameter and thickness by utilising a micrometre and after replacing each single tablet into a tablets hardness tester machine, the crushing capacity was detected in KGF also the tensile strength, hardness and density were determined.

Table 3: Tensile strength results

Formulation	F1	F2	F3	F4	F5	F6	F7 (wet granules)
Glycine percentage %	16	21	11	30	5	40	21
Hardness(kgF)	3 ± 0.221	3.25 ± 0.126	2.89 ±0.0575	4.21 ± 0.233	2.66 ± 0.084	4.85 ± 0.126	10.96 ± 1.082
Tensile strength (MPa)	0.5935 ±0.0382	0.6471 ±0.0180	0.5768 ± 0.0122	0.8747 ± 0.0337	———	1.0278 ± 0.0201	2.1620 ± 0.2019
Tablet density (kg/ M^3)	6.228.349	6.361.047	6.252.576	6.343.588	_____	5.804.539	6.171.593

According to the role of glycine in the improvement of the hardness and the strength of tablets, it was expected that the more glycine the tablet contains, the harder and stronger the tablets [25]. That is observed from the results (Table 3), where F6 had the highest hardness with an average of 4.85 KgF and tensile strength 1.0278 MPa since it had the most glycine in with percentage 40%, while it was expected that F5 had the lowest hardness and tensile strength because it had the lowest percentage of glycine 5% but unfortunately the test for tensile strength has not been done for this formulation because the number of tablets was not enough. Therefore, F3 was considered the lowest hardness with an average 2.89KgF and tensile strength 0.5768 MPa since it had the lowest amount of glycine with a percentage of 11%. Furthermore, F1, F2 and F4 had percentages of glycine as 16%, 21% and 30% respectively so they had hardness/tensile strength with averages of 3KgF/0.5935 MPa, 3.25KgF/0.5935 MPa and 4.21/0.8747 MPa respectively.

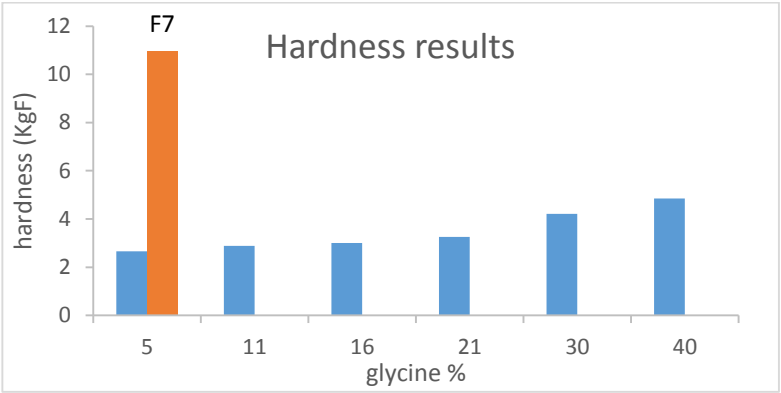

Fig. 6: Hardness results related to percentage of glycine

Focusing on (Figure 7), F7 wet granules (the orange column) recorded great hardness with an average of 10.96 kgF and tensile strength 2.1620MPa since it had polyvinyl-pyrrolidone as a binder with an amount of 4g. Overall, the results clearly reflect the important function of glycine in improving the hardness and tensile strength of tablets.

4.5. Friability

After choosing randomly 20 tablets from every single formulation and weighing them together before replacing them into the friability machine where the number of rotations was 100 times and the speed was 25rpm, then the 20 tablets were weighed once again and the results of the friability test were recorded as it is mentioned in table 4.

Table 4: Friability testing, initial mass and mass loss results

Formulation	F1	F2	F3	F4	F5	F6	F7
Glycine %	16	21	11	30	5	40	21
Initial mass(g)	**5.8362**	**6.065**	**6.3429**	**6.010**	**6.271**	**6.309**	**6.277**
Mass loss(g)	**0.0540**	**0.0612**	**0.0620**	**0.0288**	**0.0627**	**0.0172**	**0.0147**
1% limit	**0.0583**	**0.0656**	**0.0634**	**0.0601**	**0.0630**	**0.0630**	**0.0627**

According to the British Pharmacopeia, which provides for "the maximum loss of mass should not be more than 1.0 %". For all the formulations the tablets passed the test and all of them were within the limits.

Focusing on the results of this test (Table 4), it is obvious that there was a strong relationship between the amount of glycine and the strength of tablets where the more glycine the formulation contained, the harder the tablets. Therefore, F6 had the highest strength since it had the highest amount of glycine, while F5 had the lowest strength since it had the lowest amount of glycine.

Furthermore, F7 recorded a great value of strength and lost the lowest weight of 0.0147g since it is hadpolyvinyle-pyrolidone.

4.6. Uniformity of content

In order to determine the quantity of drug each tablet contains, the UV spectroscopy was utilised where the wavelength was 270nm to measure the absorbance and by arranging the formula of the line using the calibration curve (Figure 6) and Multiplying the result up by 50 (dilution factor). After selecting three tablets randomly from every single formulation, the average weight of them was recorded by using the four-digit balance. The determined quantity of drug for every tablet individually was then analysed versus the average quantity limits for the related formulation. According to the British Pharmacopeia to pass this test every single content should be between 85% and 115% of the mean of content and the preparation cannot be passed in two cases. Firstly, if more than one single content deviates from these limits. Secondly, if one single content is not between 75% and 125% of the mean of the content.

Table 5: Average of drug content

	F1	F2	F3	F4	F5	F6	F7
Average of drug content %	99.87 ± 1.1304	101.7 ± 2.6216	102.25 ± 0.8578	100.02 ± 1.0729	105.45 ± 0.7812	108.63 ± 0.5153	113.84 ± 0.8818

Focusing on the previous table, it it's recognised that the dispersion of drug throughout the tablets of all formulations is inside the limits according to the British Pharmacopeia. Therefore, it is considered that all the tablets of the seven formulations are passed the uniformity of content test.

4.7. The pH of the phosphate buffer solution

The pH meter (model 3505) was used to test the pH of phosphate buffer solution after the dissolution test and the result was 7.12.

***4.8. In vitro* dissolution testing**

For measuring the drug release percentage of the theophylline tablets, a linear calibration curve is constructed (figure 6) for different theophylline concentrations followed by measuring the released theophylline during the dissolution of the tablets at different time intervals. The following graphs display the studied 7 tablets formulations, comprising 6 formulations made by direct compression and one made by wet granulation. Each formulation is done as triplicate.

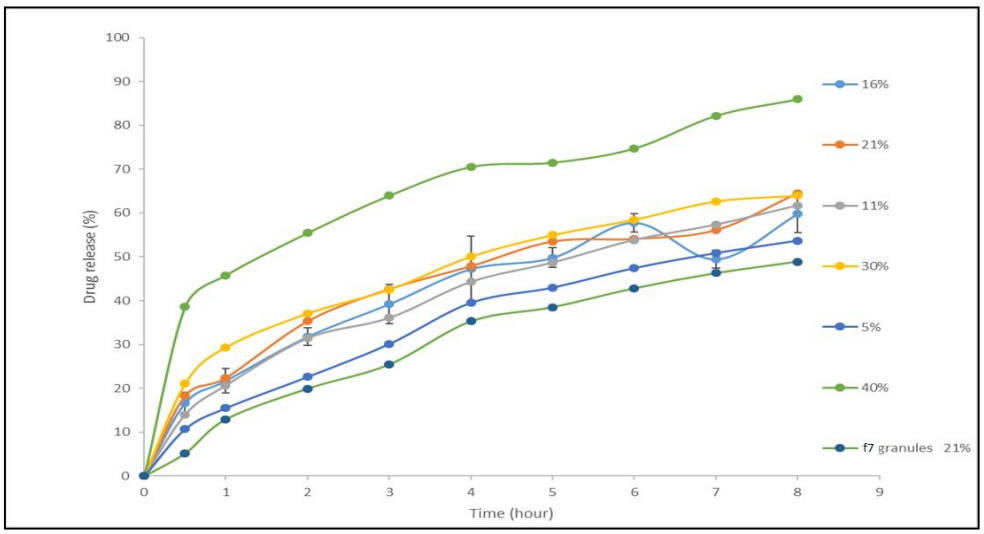

Fig. 8: Percentage drug release over 8 hours during dissolution test

On increasing glycine/guar gum ratio, it is clear that the higher amounts of glycine and lower amounts of guar gum enhance the theophylline release. The highest curve (40 % glycine & 20 % guar gum) shows the release of approximately 45 % of the drug by the first hour, which is not preferred for the extended release formulations. The lowest curve (5 % glycine and 55 % guar gum) describes the slowest release such that around 50 % of the drug is released during the 8 hours, which enables the table to be administered every 16 hours. This formulation is the best formulation of the glycine and guar gum blends for the sustained release purposes allowing for the reduction of the dose frequent administration. However, on adding a new excipient like the polyvinyl-pyrolidone (PVP), it is found that it can make a steeper reduction in the profile release rate of the 21 % glycine and 39 % guar gum formulation. Before adding the 4 % PVP, almost 60 % of the drug is liberated over 8 hours but fortunately, 40 % of the drug is released after the PVP addition. Addition of the PVP enables the release of the complete theophylline dose over 20 hours and consequently, this tablet can be administered once daily. According to the aforementioned results, the formulation including the glycine, guar gum and PVP blends, is considered a good model for the sustained release tablets which achieves the overall objective of the project.

4.9. Swollen and erosion index

Table 6: Percentage swelling and erosion for formulations after 8 hours

Formulation	Tablet	The initial mass of tablet (mg)	Swollen percentage (%)	Eroded percentage (%)
F1	1	316.3	328.6	33.2
	2	315.9	333	45.2
	3	313.4	341.2	39.1
			Average = 334.26	**Average = 39.1**
F2	1	315.5	288.58	40
	2	314.8	315.95	42.4
	3	316.8	288.7	36.4
			Average = 297.63	**Average= 39.6**
F3	1	308.3	388	54.6
	2	306.6	404.7	59
	3	304.4	350.7	32.7
			Average = 378.46	**Average = 48.7**
F4	1	300.5	310.9	57
	2	301.4	315.5	54.8
	3	304.0	333.5	52.2
			Average 319.96	**Average = 54.6**
F5	1	310.7	315.2	34.6
	2	310.9	349	22.6
	3	318.4	345.5	22.3
			Average =336.56	**Average = 26.5**
F6	1	306.7	280.4	75.8
	2	314.1	247	77.5
	3	309.9	252.6	75.6
			Average = 260	**Average= 76.3**
F7	1	311.3	343.5	40.5
	2	314.1	326.5	39.8
	3	316.4	358.3	41.7
			Average = 342.7	**Average=40.6**

The above table illustrates the relation of the swelling factor to the concentration of guar gum and glycine such that decrease in glycine or increase in guar gum increases the swelling factor. This is due to the competition between glycine and guar gum for the water uptake in the gel, which ends finally by the water uptake for the glycine more than the guar gum according to the ionization properties of glycine [26]. The effect of the glycine ionization was also discussed before by Beneke team in 2009. This is proved by the formulations having low amounts of glycine and high amount of guar, which mainly depend on the high swelling index of guar gum and this principle was discussed before by Patel in 2014.

Increment of glycine ratio enhances the matrix erosion in direct proportion manner. This also can be explained by the reduction of the guar gum in the formulation matrix, which participates in slower erosion [27]. This clarifies the higher swelling and the lower erosion by decreasing the glycine and increasing the guar gum to form a stronger gel in order to design better-extended release formulations.

On the other hand, the hydrophilic property of the PVP increases dramatically the swelling efficiency of the matrix but causes an anegligible rise in the erosion. The PVP increases the swelling of the matrix of formulation 2 from 297.6% to 342.7% and the erosion from 39.6% to 40.6%.

4.11. Kinetic models

Table 7: The rvalues for all tested models

Model	F1	F2	F3	F4	F5	F6	F7
Zero order	0.8605	0.8806	0.9304	0.8687	0.9492	0.7741	0.9597
First order	0.9031	0.9572	0.9921	0.9836	0.9882	0.9757	0.9839
Higuchi	0.9695	0.9874	0.9984	0.9890	0.9900	0.9445	0.9804
Hixson-crowell	0.8962	0.9277	0.9827	0.9267	0.9712	0.9055	0.9767
Korsmeyer-peppas	0.9767	0.9867	0.9975	0.9958	0.9951	0.9953	0.9785

According to the results of theophylline tablets dissolution, they were used to construct different kinetic models comprising zero order, first order, Higuchi, Hixson-Crowell and Korsmeyer-Peppas.

For the zero order, all the data show that most of the formulations obey the zero-order kinetics displaying high r-value and good linearity. F7 shows the best release profile with r (0.9597) by F5 (0.9492) and F3 (0.9304). However, the other models show better

linearity than the zero for all the formulations. Regarding the first order, the release results are better plotted by F3 (0.9921) followed by slight reductions in the other formulations except for F1 (0.9031). concerning the higuchi model, it is the best than all the other models as it represents good linearity equations for the theophylline diffusion from all the newly designed matrices, by achieving the highest linearity release for F5 (0.99) and at the same time, all the other formulations acquired r values above 0.9.

On the other hand, Hixson-Crowell model produced r good results on changing the surface area and the diameter of the tablets. It is obvious that the erosion of the matrices of all the formulations can have linear plotting with high r values for all the formulations except F1 (0.8962) taking again in consideration that F3 (0.9827) and F7 (0.9767) have the largest r-values. Nevertheless, Korsmeyer-Peppas shows high r values for all the formulation achieving the high test value for F3 (0.9975).

Finally, it is concluded that the first order, Higuchi model and Korsmeyer-Peppas represent the best linearity equations for the theophylline release from the newly designed matrices as all their r values are above 0.9.

5. CONCLUSION

In this study guar gum, glycine and PVP are used in different ratios to design an extended release profile for theophylline. Higher glycine ratios increase the matrix erosion in direct proportion manner which is associated with the reduction of the guar gum in the formulation matrix. This proves the higher swelling and the lower erosion indices by reducing the glycine and increasing the guar gum to design stronger gel for better-extended release formulations. Additionally, the hydrophilic property of the PVP improves the swelling efficiency of the matrix accompanied by a negligible change in the erosion.

The formulation matrix (5 % glycine and 55 % guar gum) shows the slowest release out of the glycine and guar gum blends by releasing approximately 50 % of the drug is released during the 8 hours, which can help for the tablet administration every 16 hours. Nevertheless, polyvinyl-pyrolidone (PVP) addition to the matrix is valuable at it enables theophylline dose release over 20 hours and thus, this tablet can be administered once daily. The formulation matrix containing the glycine, guar gum and PVP, is considered the best model for the sustained release tablets, which achieves the overall aim of the project.

6. NOTES

- The glycine was used in preparing F1, F2, F3, F4, F5 was with a reagent grade of 98.5%, while the glicine was used in preparing F6 and F7 was with a reagent grade of 98%.
- The formulation number 5 was performed with the same amount of ingredients in the form of dry granulation but it has been cancelled since its performance and the hardness results were the same as it was in the form of direct compression and it could not achieve the desired results where it was expected that the results of hardness should have been high.
- Another trial was performed with formulation number 6 in the form of wet granulation where 25 ml of 5% PVP was added to the ingredients as a liquid binderin hopes of decreasing the drug release but the trial has been cancelled because during the dissolution test the absorbance of the first two hours was too high contrary to what was expected where the aim of the trial was to design tablets with prolonged drug release over time.

7. FUTURE WORK

For more improvement of the current project formulations, the wet formulation is recommended instead of the direct compression technique according to the previous studies, wet granulation enhances the hardness of the modified release tablets. Using glycine with wet granulation may prolong the release profile of drugs. Another modification must be taken in consideration such that other different ratios of guar gum and glycine must be used in the extended release formulations, provided that these ratios can show a significant difference between the tests like tensile strength, hardness, swelling factor, erosion rate and drug release. Changing the ratios of guar gum and glycine in the wet granulation must be associated with the addition of various biocompatible hydrophilic materials like PVP, carbopol and polyethene glycol to investigate the physicochemical changes in the tablet matrices.

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APPENDIX