Annals of Phytomedicine, Special Issue 1, AU Pharmacon (TRIPS-2022): S72-S78, 2022

DOI: http://dx.doi.org/10.54085/ap.trips.2022.11.1.8

Annals of Phytomedicine: An International Journal

http://www.ukaazpublications.com/publications/index.php

Print ISSN : 2278-9839 Online ISSN : 2393-9885

Original Article : Open Access

Development of a suitable dissolution media for class IV natural compound: Mangiferin

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Article Info

Article history

Received 9 August 2022

Revised 10 September 2022

Accepted 12 September 2022

Published Online 30 October 2022

Keywords

In vitro dissolution

BCS class IV drug

tween 80

Mangiferin

UV-spectrophotometer

Abstract

The current research explain how to design a of dissolution method for a natural bioactive compound, mangiferin, which is a class IV drug. 0.1N HCl +1% tween 80, pH 4.5 acetate buffer, pH 6.8 phosphate buffer along with 1% tween 80 were employed as a dissolution medium, the effect of the apparatus type evaluated. The test samples were examined by using UV-Visible spectrophotometer at a lambda max of 282 nm.The results confirmed that drug has better release in phosphate buffer 6.8 + tween 80 by using paddle at a speed of 100 rpm.The conditions applied for test are pH 6.8 phosphate buffer + tween 80 with paddle at 100 rpm speed.

1. Introduction

Development of a suitable dissolution media for poor soluble drugs becomes a challenge for pharma researchers. Dedication of *in vitro* drug launch and dissolution profile may be very critical for making sure batch-to-batch tremendous control and to optimize formulations at the same time as drug development (Tiago Rafael Sausen *et al*., 2017). Because the dissolution is the rate controlling step *in vivo* studies, there is much emerge for developing an appropriate dissolution medium (Juan Chen *et al*., 2022). The suitable dissolution media can be designed for a poorly soluble drug by enhancing the volume of aqueous media, removal of dissolved drug, co solvents or by the addition of surfactants or by changing the pH (Pande and Biyani, 2017). Among all these methods, addition of surfactants and changing the pH is the simple and resemble gastrointestinal fluid environment (Vijayalaxmi *et al*., 2022). In current research, work solubility of mangiferin was enhanced by the addition of co-solvents or surfactants to the dissolving medium. The optimized dissolution media employed for testing the *in vitro* dissolution studies of prepared dispersions. The chosen dissolution media became used to observe the dissolution method of mangiferin tablets (300 mg).

Mangiferin, a poorly water soluble drug, which comes under BCS class IV drug and shows a log P: 2.42 and a pKa: 0.85. Low water soluble drugs would not have better dissolution, even we create pH in physiological range, this leads to use of surfactant.

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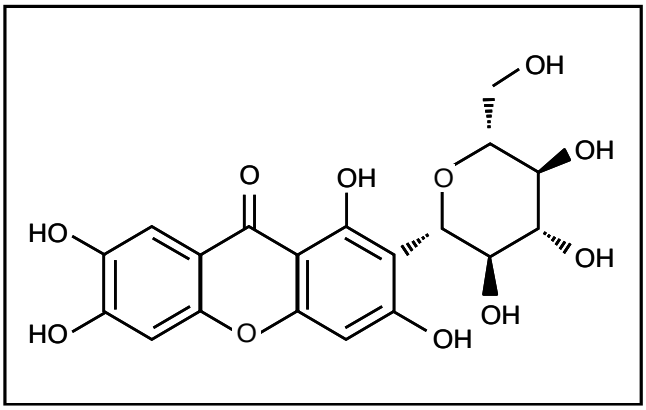

Figure 1: Chemical structure of mangiferin.

2. Materials and Methods

2.1 Materials

Mangiferin was extracted and isolated in our laboratory of Srikrupa Institute of Pharmaceutical sciences. Sodium lauryl sulphate and tween 80 was purchased from S.D. Fine Chemicals, Mumbai. All other materials used were of analytical grade.

2.2 Extraction of mangiferin

2.2.1 Soxhlet extraction

Leaves were collected from medicinal garden and dried at room temperature. The dried leaves made into powder and sieved to get uniform powder. 30 g of dried mango leaves powder was weighed and placed in a Soxhlet apparatus. 300 ml solvent like methanol was added and extraction was done for 48 h. After 48 h, methanol

extract was collected and distilled off. The dried extract was analyzed by HPLC to find concentrations of extracted mangiferin. The completion of extraction process was confirmed by performing iodine vapor test. A small drop is placed on a TLC plate with capillary tube and placed in iodine chamber. The colorless spot confirms the end of reaction (Figure 2).

2.3 Mangiferin isolation from crude extract

The crude extract collected from Soxhlet extraction method was fractionated with various solvents like petroleum ether, methanol and ethyl acetate. Fractionization by using ethyl acetate at 1:3 proportions on magnetic stirrer gives good result.

Figure 2: Extraction of mangiferin.

2.4 Kneading method

Accurately weighed amount of mangiferin and sodium starch glycolate in the concentration of 1:1, 1:2, 1:3, 1:4 and 1:5 was taken in a mortor. A small amount of solvent was added and kneaded for 30 min.The formed paste was dried in oven for 24 h at 40°C. The dried powder was size reduced and screened through sieve no 60 and stored in a tightly closed container (Naseeb Basha *et al*., 2015).

2.5 Evaluation of mangiferin solid dispersions

The percentage of yield was calculated to understand the efficacy of solid dispersion technique which helps to select optimum method for production. Solid dispersion of mangiferin collected and weighed to calculate yield from the following equation:

$$\% \text{ practical yield} = \frac{\text{practical yield}}{\text{theoretical yield}} \times 100$$

2.6 Drug content

10 mg equivalent weight of solid dispersion weighed and dissolved in 10 ml methanol. 1 ml of aliquots withdrawn and diluted into 10 ml with distilled water. The prepared sample filtered through what man filter paper and assayed for mangiferin spectrophotometrically by UV at 282 nm by using methanol: water (1:1 ratio) as blank. By using calibration curve using drug content was calculated. Calibration curve was constructed in the range of 100 to 500 microgram/ml. % drug content was calculated from the following equation:

$$\% \text{ Drug content} = \frac{\text{Practical amount of solid dispersion}}{\text{theoretical amount of solid dispersion}} \times 100$$

2.7 Solubility studies

The solubility studies of mangiferin was performed in water or in cosolvents or wetter in water at 37°C Mangiferin (50 mg) was further to 50 ml of water in iodine flask and unbroken in magnetic stirrer and temperature maintained as 37°C for 24 h. The resolution is filtered through Whatman paper and clear filtrate was analyzed by ultraviolet illumination at 282 nm against blank solution.

2.8 Fourier transforms infrared (FT-IR) study

Fourier transform infrared spectra of pure drug, sodium starch glycolate and solid dispersion was performed using Shimadzu IR Tracer-a hundred (Kyoto, Japan). 2-3 mg of sample was blended with 400 mg of potassium bromide and compressed into transparent disc using hydraulic press 6-8 lots strain. The samples were scanned in range of 500 to 4000 cm^{-1}.

2.9 Pre-compression evaluation

Based on apparent solubility studies, the formulation code with higher solubility was chosen for the event of solid dispersion. The flow characteristics of powder sample were evaluated to confirm the effectivity of pill.

2.9.1 The angle of repose

The maximum angle between height of the pile and plane surface is called as angle of repose. The angle of repose is indicated θ by and calculated by the following formula:

$$\text{Tan } \theta = h/r$$

where, h is height of pile, r is the radius

If, the angle of repose is less powder will have better flow properties, and the common angle of repose values form 25 up to 35° show excellent to good flow properties.

2.9.2 Compressibility index (Carr's index)

It is a parameter used to determine flow properties of powder. It is expressed in percentage and calculated by the following equation:

$$\text{Carr's index } (\%) = (D_t - D_b)/D_t \times 100$$

2.9.3 Formulation of mangiferin solid dispersion tablets

The solid dispersion of prepared solid dispersion was prepared by using direct compression. 50 mg equivalent solid dispersion weighed and mixed with excipients including microcrystalline cellulose used as binding agent, Sodium starch glycolate used as a disintegrating agent, magnesium stearate (0.5% w/w) used for lubrication, talc (1.5% w/w) used as a bulking agent and lactose monohydrate used as a filler to alter the burden of the drugs into 300 mg. The powder blend was compressed into a tablet using tablet compression machine (Schemazu) equipped with an eight mm round flat punch set. The prepared tablets preserved in an airtight container.

2.10 Evaluation of tablets

2.10.1 Thickness of tablet

The tablet thickness was evaluated by using vernier calipers. The common values have been calculated. The thickness of a tablet

needs to be managed inside 5% variant of a fashionable fee depending on the scale of the tablet.

2.10.2 Weight variation test

Weight variation test was conducted by taking 20 tablets randomly. Individual weight of each tablet taken and then collectively, the common weight of the pills and per cent of weight variant have been calculated. The USP limit for % deviation is 7.5 % for uncoated drugs weighing a 100-324 mg and no longer extra than two of the character weights of drugs should deviate from the common weight.

2.10.3 Tablet hardness

The hardness of tablets was determined by the use of a hardness tester (Pfizer). The amount of force used to break the pill became measured in kg and a mean cost changed into calculated.

2.10.4 Tablet friability

20 tablets were selected randomly from the batch and dropped into friabilator. The friabilator was rotated at 25 revolutions per min for 4min. After rotations, the tablets were collected and weighed again for calculation of friability. Tablets having less than 1% friability was taken into consideration for acceptance according to USP.

Friability% = (W1-W2)/W1 × 100

2.10.5 Drug content determination

Ten tablets were taken randomly from batch, placed in mortor and make powder. Amount equivalent to 10 mg of mangiferin was dissolved in 25 ml methanol by way of sonication for 15 min and filtered through whatmann filter paper. Suitable dilutions has been made, the samples were analyzed spectrophotometrically using UV-visible spectrophotometer at 282 nm.

2.10.6 *In vitro* dissolution studies

In vitro dissolution studies of prepared tablets were studied using USP type II paddle type apparatus at a speed of 100 rpm by maintaining the temperature 37°C. The volume of dissolution media used is 900 ml. The dissolution media was selected based on solubility studies 5 ml of samples were withdrawn at each time interval and analyzed spectrophotometrically at 282 nm.The withdrawn sample was replaced again with fresh media. The same volume of dissolution media was maintained until the end of dissolution studies. In this current study, solubility studies were considered as a basis for the designing of dissolution media. As the mangiferin is poorly soluble in water, solubility studies were done using 0.25, 0.5, 1.0% tween 80, phosphate buffer (pH 6.8 and pH 7.4) and pH 1.2.

Phosphate buffer solutions were prepared by the Indian Pharmacopoeia. For preparation of 6.8 phosphate buffer, 50 ml of 0.2M potassium dihydrogen was mixed with 22.4 ml of 0.2 M sodium hydroxide. Volume makes up to 200 ml with distilled water.

3. Results

3.1 Preparation of solid dispersions

Solid dispersion was prepared by using solvent evaporation method, kneading method and physical mixture method. Among all the methods, kneading method given better results, mangiferin used as a drug and sodium starch glycolate used as a polymer. In the present research, five formulations were prepared by using the ratios 1:1, 1:2, 1:3, 1:4 and 1:5. The final dispersion is in yellowish fine powder (Table 1).

Table 1: Preparation of solid dispersion of mangiferin

Formulation code	Drug: Carrier D:C	Weight of the drug (mg)	Weight of the carrier (mg)
KMSSG-1	1:1	100	100
KMSSG-2	1:2	100	200
KMSSG-3	1:3	100	300
KMSSG-4	1:4	100	400
KMSSG-5	1:5	100	500

3.2 Percentage yield

The percentage yield was found to in the range of 54.9-95.2 %.The greater yield was found to be 95.2% in formulation with 1:5 ratio of sodium starch glycolate by kneading method.

3.3 Drug content

Drug content was found in the range of 96.63-99.63 %, which ensures that the employed method is suitable for the preparation of solid dispersion with high content uniformity. The highest % drug content was found 99.63% in KMSSG-5 formulation.

3.4 Precompression parameters

The precompression parameters of prepared solid dispersions like angle of repose, bulk density, tapped density, hausner ratio, carr's index and solubility were determined. Compare to other methods kneading method, given better results along with sodium starch glycolate as carrier (Table 2).

Table 2: Precompression parameters of the powder blend of mangiferin containing sodium starch glycolate by kneading method

Solid dispersion code	Angle of repose (q)	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Hausner's ratio	Carr's index (%)	Solubility (mg/ml)
PMSSG-1	41.0 ± 0.36	0.324 ± 0.01	0.327 ± 0.02	1.25 ± 0.01	14 ± 0.08	0.216 ± 0.007
PMSSG-2	39.0 ± 0.13	0.327 ± 0.02	0.339 ± 0.03	1.29 ± 0.01	16 ± 0.02	0.322 ± 0.011
PMSSG-3	35.0 ± 0.02	0.329 ± 0.02	0.341 ± 0.03	1.25 ± 0.02	18 ± 0.08	0.462 ± 0.009
PMSSG-4	33.0 ± 0.22	0.234 ± 0.04	0.359 ± 0.01	1.37 ± 0.12	21 ± 0.04	0.591 ± 0.006
PMSSG-5	31.0 ± 0.14	0.237 ± 0.02	0.365 ± 0.02	1.52 ± 0.01	23 ± 0.06	0.791 ± 0.008

3.5 Evaluation of solubility

All solid dispersions of mangiferin with sodium starch glycolate have improved aqueous drug solubility compare to pure mangiferin. The solubility of mangiferin at 25°C is 0.057 mg/ml. Pure drug solubility was compared with solid dispersion solubility prepared with sodium starch glycolate by kneading method. Compare to all solid dispersion KMSSG-5 (1:5 ratio prepared by KNEADING method) have the highest solubility results; 0.790 mg/ml confirms that the solubility enhanced about 14-fold as compared with that of pure mangiferin. So, KMSSG-5 was selected for the preparation of tablets (Table 3).

Table 3: Apparent solubility of mangiferin

Medium	Solubility µg/ml (n=3)
Water	57
0.1 N HCl	50
pH 6.8 + 0.25% tween 80	65
pH 6.8 + 0.5% tween 80	185
pH 6.8 + 0.75% tween 80	300
pH 6.8 + 1.0% tween 80	790
pH 7.4 + 0.25% tween 80	150
pH 7.4 + 0.5% tween 80	250
pH 7.4 + 0.75% tween 80	300
pH 7.4 + 1.0% tween 80	348

3.6 Fourier transforms infrared study

FTIR spectrum of isolated mangiferin compound have the peaks at 3367 cm^{-1}, indicated presence of secondary OH- bond, peak at 2936 cm^{-1} showed presence of C-H anti-symmetric stretching, peak at 2891 cm^{-1}, 1648 cm^{-1} and 1255 cm^{-1} indicated presence of C-H parallel stretching, C-O stretching, and C-O bond (Figures 3,4 and 5).

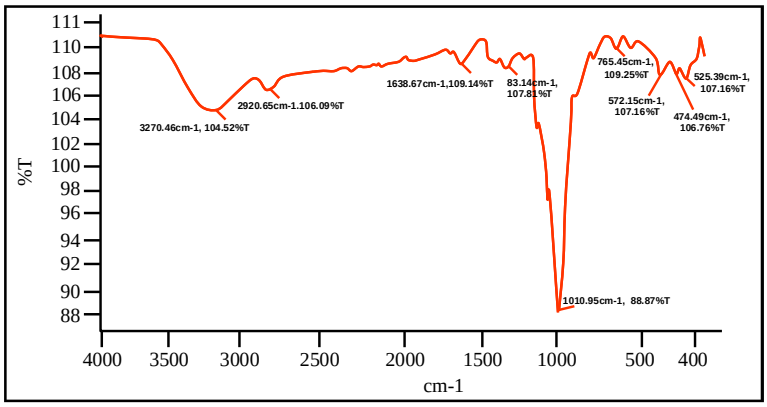

Figure 3: FTIR spectra of pure drug.

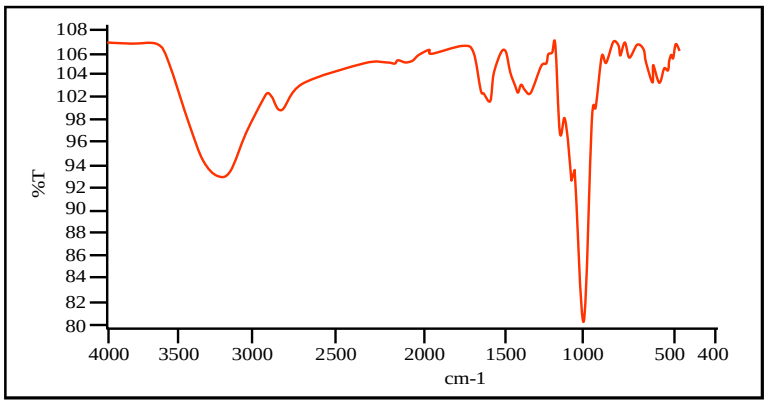

Figure 4: FTIR spectra of sodium starch glycolate.

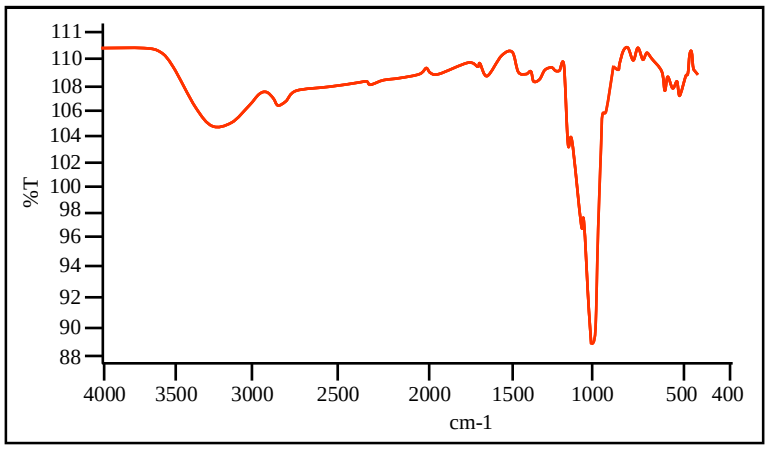

Figure 5: FTIR spectra of solid dispersion.

3.7 *In vitro* dissolution studies

In vitro dissolution studies were conducted by using USP type II paddle type apparatus in 900 ml pH 6.8 Phosphate buffer along with tween 80 for 1 h. The maximum amount of drug was released (Figure 6).

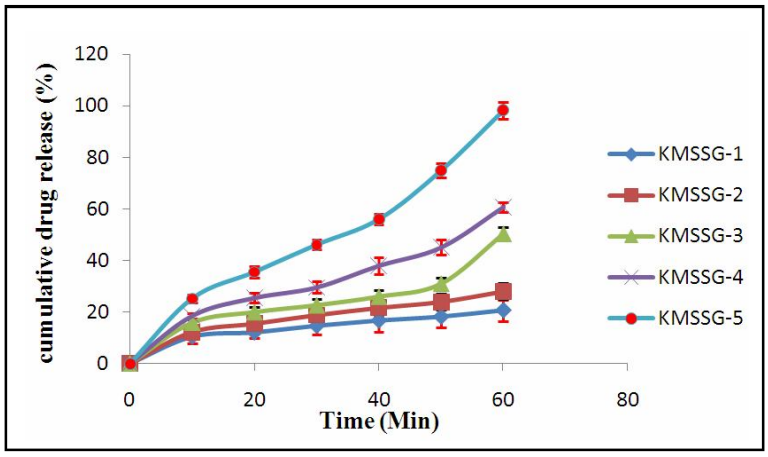

Figure 6: *In vitro* drug release of prepared tablets in pH 6.8 phosphate buffer and tween 80.

3.8 DSC studies

As discussed in previous researches, mangiferin is a poorly soluble xanthenes' compound which is having partition coefficient log P of 2.5, but it is having strong intra and intermolecular hydrogen bonds. Due to strong hydrogen bonds, it is in crystalline form which makes the drug to difficulty in solubility. Generally, solid dispersion was used to enhance the solubility of poorly soluble drugs which change the compound from crystalline state to amorphous state. Differential scanning calorimeter was studied to understand the melting point and crystalline profile of powdered mangiferin, physical mixture of sodium starch glycolate and mangiferin. The DSC curve of mangiferin has a single endothermic peak at 282 mm which is confirming that the crystal melting factor. The DSC thermogram curves of the prepared stable dispersions, did not show any obvious endothermic peak around the melting factor of mangiferin, suggesting that mangiferin may also lose its crystalline in the starch glycolate polymer matrix. Mangiferin may exist in the amorphous ground inside the SD, which is consistent with our previous observation. Our result suggests that mangiferin in SD maintained an amorphous nation after rotation to similarly verify the alternative physical nation of mangiferin after entrapment in a sodium starch glycolate matrix (Figures 7 and 8).

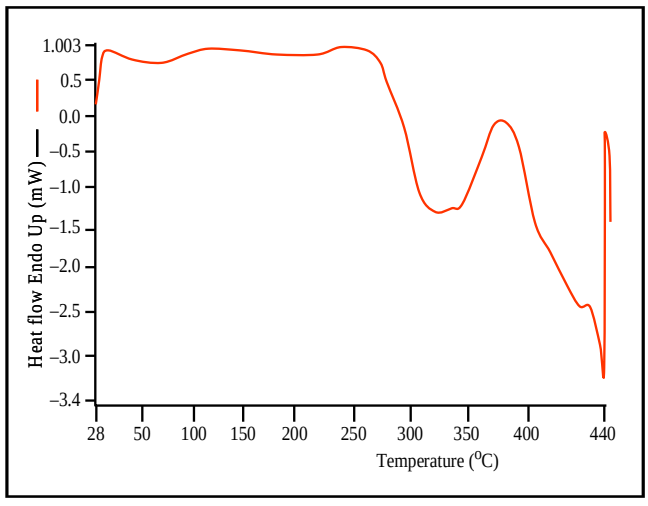

Figure 7: Differential scanning calorimetry of pure compound.

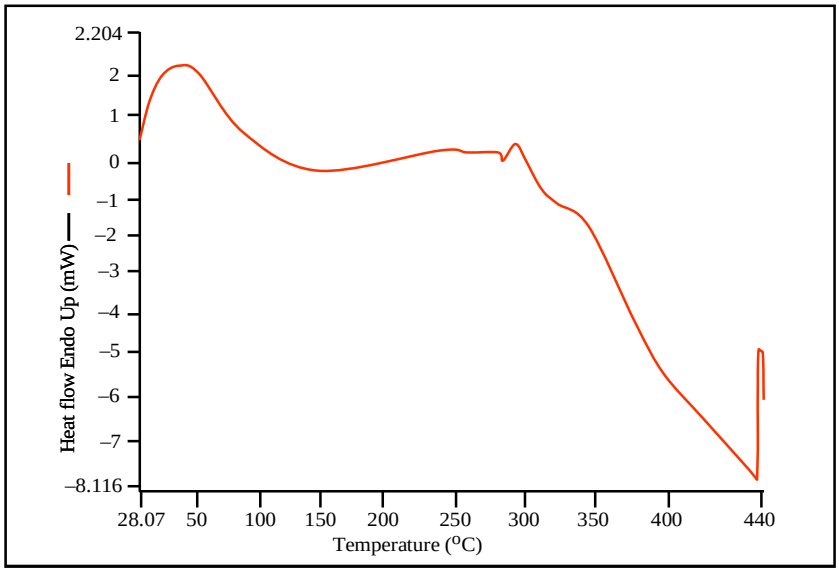

Figure 8: Differential scanning calorimetry of solid dispersion.

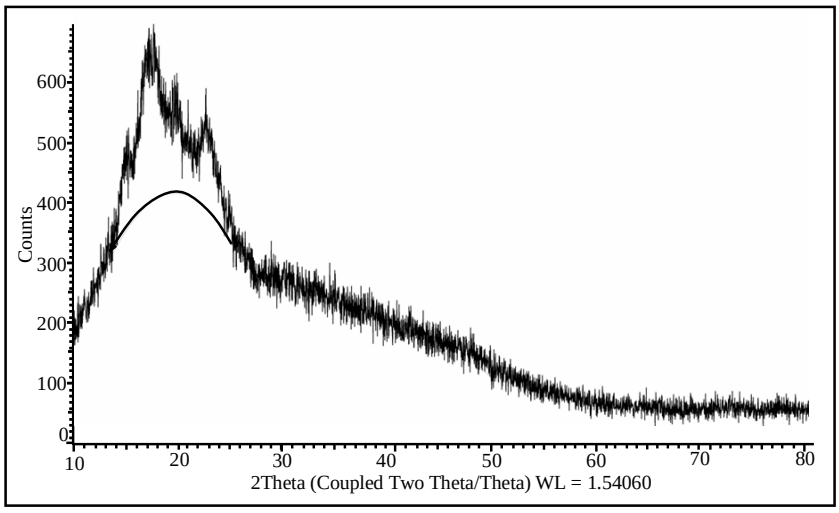

Figure 9: X-Ray diffraction patterns of pure drug.

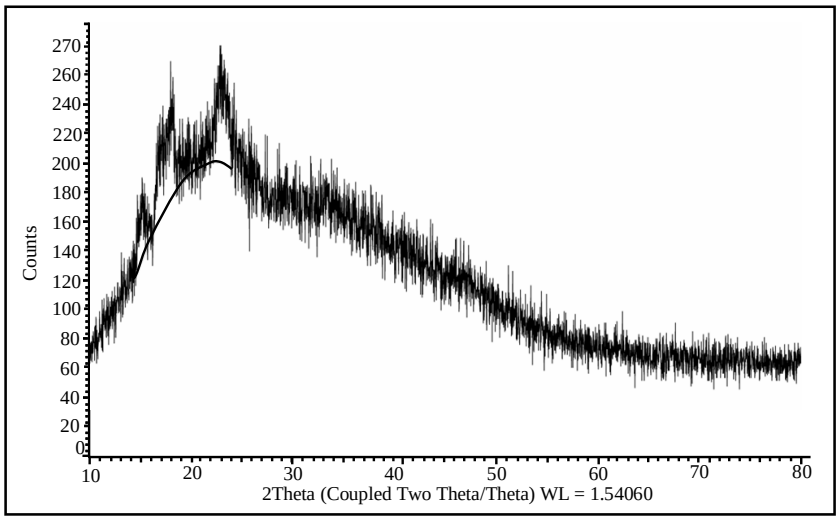

Figure 10: X-Ray diffraction patterns of solid dispersion.

3.9 X-ray diffraction studies

XRD was used to encounter crystallization houses. The XRD pattern of the SSG polymers showed no full-size diffraction peaks, which is consistent with the amorphous nature of these three acrylic polymers as previously suggested. The halo XRD pattern of the mangiferin SDs indicates that there is no crystalline compound, thus confirming the DSC claim that within all 3 acrylic polymer-based SDs, mangiferin exists in amorphous nation instead of crystal country (Figure 6).

4. Discussion

In this study, mainly we focused on development of suitable dissolution media for poorly soluble drugs. Mangiferin sold dispersion is prepared for enhancement of solubility. The solubility of mangiferin was increased in kneading method by using sodium starch glycolate as a carrier in 1:5 ratios. There is 14 fold increase (0.79 mg/ml) in solubility compare to pure drug (0.057 mg/ml). Based on solubility, study the optimized formulation was used for the *in vitro* drug release studies. *In vitro* drug release was greater in pH 6.8 phosphate buffer along with 1% tween 80. The drug release was 98.3% in 1 h. So, phosphate buffer with 1% tween 80 confirmed as suitable dissolution media for mangiferin drug.

Differential scanning calorimeter was conducted to understand the melting point and crystalline of mangiferin. The DSC curve of mangiferin has a single endothermic peak at 282 mm which is confirming that the crystal melting factor. The DSC thermogram curves of the prepared stable dispersions did not show any obvious endothermic peak around the melting factor of mangiferin, suggesting that mangiferin may also lose its crystalline in the starch glycolate polymer matrix. XRD was used to encounter crystallization houses. The XRD pattern of the SSG polymers showed no full-size diffraction peaks, which is consistent with the amorphous nature of these three acrylic polymers as previously suggested. The halo XRD pattern of the mangiferin SDs indicates that there is no crystalline compound, thus confirming the DSC claim that within all 3 acrylic polymer-based SDs, mangiferin exists in amorphous nation instead of crystal form.

5. Conclusion

The results of current research confirmed that mangiferin is having greater and better dissolution studies in pH 6.8 phosphate buffer and 1% tween 80 at a speed of 100 rpm. USP type II paddle type was used as apparatus and volume of dissolution media is 900 ml. The withdrawn samples were analyzed spectrophotometrically at 282 nm by using UV visible spectrophotometer. The formulation shown highest drug release in pH 6.8 phosphate buffer along with tween 80 is 98.3% in 1 h. So, phosphate buffer along with tween 80 can be used as a better dissolution media for mangiferin drug.

Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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Citation **Badri Nagarani and Venkata Radha Gadela (2022). Development of a suitable dissolution media for class IV natural compound: Mangiferin. Ann. Phytomed., Special Issue 1, AU Pharmacon (TRIPS-2022): S72-S78. http://dx.doi.org/10.54085/ap.trips.2022.11.1.8.**