DEVELOPMENT AND EVALUATION OF SUSTAINED-RELEASE BILAYER MATRIX TABLETS FOR AN ANTIHYPERTENSIVE DRUG WITH POOR SOLUBILITY CONTAINING NATURAL AND MODIFIED GUM

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Abstract

Objectives: The purpose of this study was to make sustained release bilayer tablets that release medicine slowly over a long period of time using Nifedipine model drug, natural and their modified form of gum like tamarind seed gum and fenugreek seed gum as release retardant. **Methodology:** Various amounts of tamarind and fenugreek seed gum natural and modified form were use and prepared eight different batches formulations of the nifedipine. The developed and optimized bilayered release matrix tablets were evaluated. **Results:** The evaluation results of nifedipine sustained release bilayer matrix tablets showed decent physical qualities. The *in-vitro* cumulative % drug releases from the tablets were exhibited best by the selected formulation same like as marketed formulation. It is clear that modified tamarind seed gum maintained a sustained release of 99.34% for up to 24 hours and modified fenugreek seed gum maintained a sustained release of 98.93% for up to 20 hours at a 40% concentration. Nifedipine tablet drug release according to the Higuchi or Hixson-Crowell model. **Conclusion:** By using the wet compression approach, the study was shown that blended hydrophilic natural and their modified form of polymers can be used to build sustained release bilayered matrix tablets for poorly soluble medicines.

Keywords: Tamarind Seed gum; Fenugreek seed gum; Natural gum, Modified gum, Bilayer tablets; Sustained Release; Nifedipine, Wet compression.

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DOI: - 10.48047/ecb/2023.12.si5a.0212

Introduction

Some gums like tamarind seed gum, pectin, chitosan, cashew gum, and xanthan gum can absorb water easily. These are used in medicine to make tablets that can slowly release drugs into the body (Maciel et al., 2006; Chivate et al., 2008; Nussinovitch, 2009; Vohra et al., 2012; Ali et al., 2013; Baviskar et al., 2013, Shukla et al., 2017). Controlled-release medicines can have many benefits, like reducing the number of times a person needs to take medicine, making it easier to follow the treatment plan, increasing the effectiveness of the medicine, lowering the chances of side effects, making the medicine more acceptable, and reducing the cost of treatment (Das and Das, 2003; Kamboj et al., 2009, Shukla et al., 2018). The design and development of an improved controlled-release product is made possible by the improvement of the physicochemical and release modifying properties of the resulting polymer by a number of natural hydrophilic polymers (Ofori-Kwakye et al., 2013, Kumar et al., 2018) and the suitable selection of polymers can help control the release profile of drugs (Fung and Saltzman, 1997). Hydrophilic matrix systems absorb water, become a gel, and eventually dissolve when exposed to water. These systems can hold a lot of medicine and are made with cheap and safe ingredients. But, they may need specific materials to control how fast the medicine is released, and it could be difficult to make them on a large scale (Aulton, 2007, Yadav et al., 2020). Scientists have made medicine tablets using natural substances called gums. They used two herbs called fenugreek and tamarind gum to make tablets that can control the amount of medicine released. These tablets work for both types of medicine that dissolve easily in water and those that don't (Shukla et al., 2019, Shukla et al., 2017, Shukla et al., 2019, Shukla et al., 2020). Fenugreek and tamarind gum are easy to find and cheap to get, so they can be used in large amounts. You can make tablets that absorb water using wet granulation or direct compression methods (Colombo et al., 2000, Shukla et al., 2019). Direct compression is a simple way to make tablets by pressing together powdered ingredients without forming granules or using an agglomeration process (Thakkar et al., 2009; Thoorens et al., 2014) and involves two sequential operations of powder mixing and table formulation.

APIs and/or excipients with acceptable flow and compressibility are required for the method. Direct compression is compatible with heat- and moisture-sensitive medications and also improves product stability because neither of these factors are involved in the process (Aulton, 2007, Kumar et al., 2018). Direct compression is the most cost-effective method for producing large batches of tablets due to the limited number of processes involved in the process (Thoorens et al., 2014). Poor flowability of powder blends, variability in tablet weight, poor content uniformity, tablets with weak mechanical properties, and poor dissolution properties are some of the main issues with direct compression brought on by the use of APIs and excipients with poor physical attributes (Hentzschel et al., 2012; Thoorens et al., 2014, Shukla et al., 2017).

The anti-hypertension medication nifedipine has a biopharmaceutics classification system (BCS) class II (low solubility and high permeability) and is only moderately water soluble (pKa= 4 approximately). It is frequently used to treat hypertension (Dastidar et al., 2000, Jain et al., 2021, Shukla et al., 2020). Formulations with a sustained release matrix are necessary for the treatment of chronic diseases like hypertension. It is essential for the long-term control and management of hypertension. According to (Shukla et al., 2020, Sharma et al., 2018), a novel film-coated sustained release dosage form using natural and modified fenugreek and tamarind seed gum can be used as a release retardant polymer for the production of controlled release dosage forms.

The weakly water soluble medication nifedipine (NFD) was produced as a sustained release matrix tablet with xanthan gum (xg), tamarind gum (TG), and fenugreek gum. They employed various dosages of the medication and the polymer; the direct compression process was used to make sustained release tablets (Shukla et al., 2022). According to these studies, both natural and modified forms of gum are useful for the production of sustained release formulations for drugs that are weakly and water soluble employing direct and wet compression methods. The current study's objective was to create nifedipine sustained release oral bilayer pills utilising various mixtures of fenugreek and tamarind seed gum that were both natural and modified. The goal was to improve the polymers' ability to adjust drug release retardant characteristics, resulting in optimised formulations of the two model pharmaceuticals with various water solubilities.

Materials and methods

Materials

We received some drugs called nifedipine as a gift from a company called Alembic in India. We was used water to extract gum from tamarind seeds and fenugreek seeds. We got microcrystalline cellulose from Lobacem Pharmaceuticals in India. We also got some other chemicals from a store at Mohanlal Sukhadia University in India. All the chemicals we used were good quality.

Isolation method of fenugreek gum (FSG)

Fenugreek seed was gathered and given a watery wash. The gum was completely released into the water after being dried in a hot air oven and the seeds were crushed, soaked in water for six hours, boiled for thirty minutes, and then allowed to stand for an hour. In order to separate the gum, the marc was taken out of the solution using a four-fold muslin cloth bag. Three times the volume of filtrate was added of ethanol to precipitate the gum. With the use of a four-fold muslin cloth, the gum was once more separated, and then dried in a hot air oven at 40°C. The pulverised dry gum was collected, put through a # 120 sieve, and kept in a desiccator until use at 30°C and 45% relative humidity (Brummer et al., 2003, Reddy et al., 2012, Shukla et al., 2019, Mehta et al., 2018).

Isolation method of tamarind gum (TSG)

The tamarind seed was gathered and given a watery wash. The tamarind seeds were then dried in a hot air oven, soaked in distilled water for a week, and the white section of the seeds were removed and crushed. To allow the gum in the tamarind seeds to completely release into the water, the tamarind seeds were crushed and steeped in water for 12 hours, then cooked for 30 minutes, and then allowed to stand for 1 hour. The gum was separated by removing the marc from the solution using a four-fold muslin cloth bag. To precipitate the gum, ethanol (in amounts three times the volume of filtrate) was then added. The gum was once more separated using a four-fold muslin cloth before being dried in a hot air oven at 40°C. The pulverised dry gum was collected and stored in a desiccator at 30°C and 45% relative humidity until use (Brummer et al., 2003, Reddy et al., 2012, Shukla et al., 2019).

Modification of isolated gum with sodium tri-metaphosphate (STMP)

I gram of STMP and 1 gramme of natural gum were taken separately and dissolved in 50 ml of distilled water in a beaker. Then, after adding the STMP solution, 1g of natural gum solution received 5ml of 0.1 N NaOH while being stirred. The 100ml reaction solutions were agitated for two hours, poured into a petridish, and dried for 24 hours at 600C.

The compound (modified gum) was pulverised after drying. used to create tablets after being sieved with a #120 aperture sieve (Brummer et al., 2003, Reddy et al., 2012, Shukla et al., 2019).

FTIR study of natural and modified gums

A Bruker FTIR spectrophotometer was used to scan 10 mg of the gum powder between the wavelength ranges of 1000 cm-1 and 4000 cm-1. We compared the spectra of natural and modified gums. Figures 1, 2, and 3 depict the FTIR spectra of natural FSG, TSG, and sodium trimetaphosphate (STMP), while Figures 4, and 5 depict the FTIR spectra of modified FSG, MTSG, respectively.

X-ray diffraction analysis (XRD) of natural and modified gums

Using X-ray diffraction (XRD), the crystalline nature of native and modified gums was assessed. A comparison of the X-ray diffraction spectra was done97.Figure No. for FSG 6, TSG 7, MFSG 8, and MTSG 9 shows the XRD spectra of natural and modified gums, respectively (Reddy et al., 2012, Shukla et al., 2019).

Compatibility studies of drug and excipients

The drug's FTIR spectra was determined and examined for the presence of distinctive drug peaks when the excipients were present, both alone and in combination. In Fig. 10–11, the FTIR spectra of the medication NFD with and without excipients are depicted. Nifedipine's DSC thermograms in its pure and combined forms are depicted in Fig (DSC spectra of NFD 12–13), respectively (Reddy et al., 2012, Shukla et al., 2019).

Preparation of blended powders

The tables show different ways of making nifedipine tablets that release the drug slowly. The ingredients include nifedipine, tamarind seed gum, fenugreek seed gum, magnesium stearate, and lactose. These ingredients were mixed together and then lubricated with magnesium stearate. The mixtures were stored for testing and then

compressed into tablets. The composition of each tablet is shown in Table 1.

Wet granulation technique for making bilayer tablets

The amount of medicine in the regular tablet and the ongoing tablet was figured out using a specific formula.

Dose calculation of nifedipine

The maintenance dose (SR) and the dose in the formulation for the instant release (IR) tablet were determined using the provided formula.

Dt = Dose (1 + 0.693 × t/t $_{1/2}$) where Dt is total dose of drug, t = time, t $_{1/2}$ = half life of drug

20 = x (1 + 0.693 × 24/2)

X = 20/9.316 = 2.14 mg (2mg approx)

Immediate release dose of nifedipine dose = 2 mg

Sustained release dose of nifedipine dose = 18mg

Formulation of sustained release bilayer matrix tablets of nifedipine

Gums, both natural and artificial, were used in the wet granulation process to create nifidipine sustained release bilayer matrix tablets.

Preparation of blends for wet granulation method

The immediate release layer and the second sustained release layer were both present in bilayer matrix tablets of nifedipine. Starch and PVP were used to prepare the immediate release layer. Different concentrations of natural and engineered seed gum are used as release retardant materials in the sustained release layer. Nifedipine bilayer sustained release matrix tablets were created using wet compression techniques. Table Nos. 1 and 2 display the composition of the immediate release layer and the sustained release layer, respectively.

Table: 1 Composition of nifedipine immediate release layer

S. No	Ingredient	Quantity
1	Nifedipine	2mg
2	PVP	5mg
3	Starch 1500	88 mg
4	Mg. Stearate	5 mg

Table: 2 Composition of nifedipine sustained release layer

SN	Bat.	NFD	TSG	FSG	MTSG	MFSG	Lactose	PVP	Mg. Ste	Total
1	A	18	80				177	15	10	300
2	B	18		80			177	15	10	300
3	C	18			80		177	15	10	300
4	D	18				80	177	15	10	300
5	E	18	160				97	15	10	300
6	F	18		160			97	15	10	300
7	G	18			160		97	15	10	300
8	H	18				160	97	15	10	300

All the quantities were taken in mg

Blends preparation of immediate release layer for wet granulation method

All excipients and the drug were correctly weighed and passed through #80mesh filters, with the exception of the magnesium stearate. The mixture was put to a plastic bag and stirred for 5 minutes after being sieved. After that, the mixture was ground into granules using a binder solution that contains 5% w/v PVP in isopropyl alcohol. Granules that were still wet were dried at a temperature of 600C in a hot air oven. The final dried granules were then passed through #80 mesh screens, and magnesium stearate was added as a lubricant. Table 4.5 lists the ingredients of the nifedipine instant release layer.

Blends preparation of sustained release layer for wet granulation method

All excipients and the drug were correctly weighed and passed through #80mesh filters, with the exception of the magnesium stearate. The mixture was put to a plastic bag and stirred for 5 minutes after being sieved. After that, the mixture was ground into granules using a binder solution that contains 5% w/v PVP in isopropyl alcohol. Granules that were still wet were dried at a temperature of 600C in a hot air oven. The final dried granules were then passed through #80 mesh screens, and magnesium stearate was added as a lubricant. Table 4.6 displays the ingredients of the nifedipine sustained release layer.

Pre-compression evaluation of blends

Angle of repose, Bulk density g/cm3, Tapped density g/cm3, Carrs index, and Hausnerratio were investigated for pre-compression parameters for blends of immediate release layer and sustained release layer for wet granulation processes.

Bulk density and tapped density

A 100 ml measuring cylinder was filled with 10 grammes of the mixture. The amount of powder was measured without moving the cylinder. It represents the majority of the gum powder's volume. Following this, the powder's volume was measured every 50 taps for a total of 300 taps. It represents the blends' tapped volume. The following formula was used to get the bulk density and the tapped density.

$$\text{Bulk density } (\rho) = \frac{\text{Weight of sample}}{\text{Bulk volume}}$$

$$\text{Tapped density } (\rho b) = \frac{\text{Weight of sample}}{\text{Tapped volume}}$$

Hausner quotient

The ratio of tapped to bulk densities was used to calculate the Hausner ratio or quotient.

$$\text{Hausner's quotient (ratio)} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Carr's index %

The following formula was used to calculate the blends' Carr's index percentage.

$$\text{Carrs index } \% = \frac{V t\rho - V\rho}{V t\rho} x100$$

Where, Vtρ= tapped density; Vρ= bulk density.

Hausner quotient

The ratio of tapped to bulk densities was used to calculate the Hausner ratio or quotient.

$$\text{Hausner's quotient (ratio)} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Angle of repose

Angle of repose was used to determine how mix powder flowed. Frictional forces between the particles are to blame for the uneven flow of powder. By measuring the angle of repose, these friction forces were measured. The following formula was used to get the angle of repose:

$$\theta = \frac{\tan^{-1}(h)}{r}$$

Where, h= height of pile; r= radius of the base of the pile and θ = angle of repose.

A burette stand was used to hold a clean, dry funnel at a 6 cm height. 10 gm of the blend powder was slowly poured down the funnel until the heap reached the tip, then the graph paper was placed on the level surface. The heap's perimeter was marked, its midpoint identified, and its radius quantified. The average height and radius were calculated after the experiment was conducted three times. Using the aforementioned formula, the angle of repose was determined.Table 3 displays the evaluation outcomes for bilayer blends of NFD pre-compression.

Compression of nifedipine bilayer matrix tablets by wet granulation method

First, the die was compressed using a single punch tablet compression machine outfitted with 8 mm round concave punches after being packed with sustained release granules. Accurately weighed immediate release layer grains were put onto this compressed sustained release layer. Then another compression was performed to create a bilayered matrix tablet

Evaluation of sustained release bilayer matrix tablets

The following factors were assessed for the bilayer matrix tablets of propranolol HCl and nifedipine(Newtona et al., 2015, Kulkarni et al., 2013, Porwal et al., 2011).

Average-weight

20 tablets were chosen at random, and a single pan electronic balance was used to measure each tablet's weight. The average weight was then determined.

Hardness test

Using a hardness tester, Pfizer determined the tablet's hardness. Kg/cm2 units were used to measure the hardness.

Friability

The plastic chamber of the Rochesfriabilator contained 20 tablets that had been weighed. The chamber was then rotated 100 times in four minutes at 25 rotations per minute. Tablets are dropped six inches away on each revolution. The tablets were taken out and weighed again after 100 rotations. The formula was used to determine friability.

$$\text{Friability } (\%) = \frac{W1 - W2}{W1}$$

Where w_1 was the initial weight of tablets before friability testing, w2 was the weight of tablets after the test.

Drug content

The prepared 10 bilayer tablets were each precisely weighed and pulverised. The drug powder was placed in separate 10 ml volumetric flasks with 10 ml of phosphate buffer pH 7.4 added and swirled continuously for 1 hour. Filtered solutions were created, and the filtrate was appropriately diluted. For nifedipine, the absorbance was calculated at -max 238 nm. Table 5 for NFD displays the findings of the examination of bilayer tablets following compression.

Dissolution studies

Using an eight station (USP) Type II dissolving equipment at 37 0.5°C and 50 rpm speed with 0.1 N HCl as the dissolution medium for 2 hours, the in-vitro drug release profile of bilayer tablets was investigated. In order to maintain the sink condition, 5 ml of the sample from the dissolution medium were removed at the designated time intervals and replaced with an equivalent amount of fresh medium. Following filtration, a double beam UVvisible spectrophotometer was used to analyse each sample at a chosen drug maximum. For each batch, this study was carried out three times. After two hours, phosphate buffer pH 7.4 was used to replace the dissolving media. Aliquots were periodically removed, and the drug content was determined using a UV-visible spectrophotometer at a chosen drug λ-max(Santhi et al., 2013, Patra et al., 2007, Sachan et al., 2017). The *In-Vitro* drug release profile of bilayer tablets of NFD are shown in Table 7.

Kinetic Studies

Characterization of kinetic release profile

We checked how quickly drugs were released from different types of tablets. We used math equations to figure out the rate and way the drugs were released. We used an equation called "zero order release" to do this.

$$Q_t = Q_0 + K_{0t}$$

This equation explains how much of a drug dissolves over time. It uses the symbols Q0 for the starting amount of the drug, Qt for the amount dissolved at a certain time, and K0 for the release rate. The equation can be expressed in first or zero order form.

$$\log Q_t = \log Q_0 + K_1 t/2.303$$

K1 is the first order release rate constant. If we plot the logarithm of the remaining drug against time, we get a straight line. This means that the drug release follows first order kinetics. To get K1, we multiply the slope by 2.303.

The dissolution data was also analyzed using Higuchi's equation. This equation is called the Higuchi model:

$$Q = K_H t^{1/2}$$

The amount of drug released over time is called Q, and KH is a number that tells us how quickly the drug dissolves. The Higuchi model explains how drugs dissolve based on diffusion and the square root of time. We can use the Korsmeyer-Peppas equation to estimate how drugs will dissolve from polymeric systems by analyzing the dissolution data.

$$M_t/M_\infty = a\, t^n$$

This paragraph is talking about how drugs are released from tablets and how to measure and understand the release process. The fraction of drug released is called Mt/M∞ and it depends on factors like release time, the type of drug, and how the drug is released. The diffusion exponent (n) is a value that helps us understand how the drug is being released. If n is less than 0.5, it means the drug is being released through a certain type of diffusion called "quasi-fickian diffusion". If n is equal to 0.5, it means the drug is being released through a different type of diffusion called "fickian diffusion". If n is between 0.5 and 1, it means the drug is being released in a way that involves both diffusion and erosion. If n is equal to 1, it means the drug is being released in a very specific way called "Case-II transport". And if n is greater than 1, it means the drug is being released in a way that is not related to fickian diffusion. There is an equation called the Hixson-Crowell equation that helps us understand how the drug is being released based on the size of the tablet.

$$Wo^{1/3} - Wt^{1/3} = kst$$

Wo denotes the beginning dosage of the medicine (Dash et al., 2004; Fatmanuar et al., 2004). At time t, Wt represents the amount of medicine still present in its dose form, and KS is a constant that takes the surface volume relation into account. The graphs are displayed as the cube root of the percentage of time till medication release.

Stability Studies

In a humidity chamber, stability tests on a few different nifedipine-containing formulations were conducted over a six-month period at temperatures of 250 C and 60% and 75% RH, respectively. On the basis of a drug content, hardness, and friability investigation, the formulations were chosen. The chosen formulations were kept in screw-capped amber bottles for six months in a humidity room at 250°C and 60% and 75% RH, respectively. Periodically, samples were obtained, and the amount of medication that had become trapped was calculated using UV spectroscopy (Bajaj et al., 2012). Tables 9 and 10 show the findings of stability investigations of a chosen formulation.

RESULTS AND DISCUSSION

Evaluation of blend for pre-compression parameters

FTIR spectra of fenugreek seed gum (FSG)

Scientists used a special tool called Infrared Spectroscopy to study Fenugreek Gum (FSG) by itself. They found that the gum had some important peaks at specific wavelengths: 1036 cm-1, 1637-1655 cm-1, 2924 cm-1, 3356 cm-1, and 1053 cm-1. These peaks represented different chemical groups in the gum. The scientists also created a picture (Figure 1) that showed these peaks using FTIR Spectroscopy.

FTIR spectra of tamarind seed gum (TSG)

We used a method called Infrared spectroscopy to study a substance called TSG. We found some important information about TSG from the study, which are shown in a picture called Figure 2. The information includes the different types of vibrations happening in TSG at different frequencies, such as vibrations from oxygen and carbon atoms.

FTIR Interpretation of modified fenugreek seed gum (MFSG)

For (MFSG), infrared spectroscopy tests were carried out. The main MFSG peaks were located at 3923.98 and 3819.08cm-1, 3731.70-3564.26 cm-1, 2931.57-2863.56cm-1, 1848.09 cm-1, 1687.44-1634.38cm-1, 1549.39-1516.0689.98-647, 07cm-1, 1279.78cm-1, 1279.78cm-1, 1154.10-1097.44cm-1, 989.52cm-1.Figure 3 displays the results, which demonstrate the presence of O-H free hydroxyl alcohol, N-H stretching, OH alcohol free, C-H stretching, C=O stretching, C=C stretching, C-H methyl stretching, C-O alkyl aryl ether, C-O primary alcohol, C=C bending Alkenes, and C-H of alkenes, respectively.

FTIR Interpretation of modified gum (MTSG)

In this study, Infrared spectroscopy was employed to investigate the modified tamarind seed gum (MTSG). The FTIR spectra of MTSG showed several peaks at different wavenumbers including 989.55 cm-1, 1099.80-1154.84 cm-1, 1394.39 - 1366.99 cm-1, 1282.98 cm-1, 1452.81-1422.62 cm-1, 1548.45-1516.64 cm-1, 1684.29-1600.56 cm-1, 2996.53-2853.25 cm-1, and 3731.70-3564.26 cm-1, which are associated with the vibrational modes of various chemical functional groups. Specifically, these peaks correspond to C=C bending alkenes, C-O secondary alcohol, OH bending, C-O alkyl aryl ether, OH bending carboxylic acid, C=C stretching, C=O carboxylic acid, C-H stretching, N-H overlap of amide with O-H, respectively. Furthermore, a broadening of the peak observed at 3564 cm-1 in the modified gum is attributed to the overlap of the N-H stretching band of the amide group and O-H stretching band. The disappearance of acetyl groups of peaks in modified TSG and FSG gum were also observed. Additionally, new peaks were detected in modified gum, which were absent in unmodified gum. These new peaks were attributed to Phosphate-II (-C-O bending) of the phosphate group of STMP, indicating the occurrence of a cross-linking reaction. The FTIR spectra of STMP and MTSG are shown in Figure 4 and 5, respectively.

X-ray diffraction analysis (XRD) of natural and modified seed gums

In this study, we utilized X-ray diffraction (XRD) to investigate the surface characteristics of natural and modified gums derived from tamarind and fenugreek. Our results indicate that the XRD patterns of natural fenugreek gum (FSG) and tamarind gum (TSG) exhibit a highly uneven surface, in comparison to the modified natural gums, which display pores and crevices, as depicted in Figures 6 and 7. Furthermore, our XRD analysis revealed that the particle size distribution of the gum powders was not uniform, with a wide range of sizes from coarse to ultra-fine particles. This disparity in particle size might be a contributing factor to the dense nature of the gum powders. We observed that the gum powders displayed a closely-packed arrangement, with smaller particles occupying the gaps between larger particles, which led to a decrease in bulkiness. The low porosity values also confirm this packing arrangement. This close packing might account for the poor flow properties of FSG and TSG.

Finally, we conducted surface characterization of natural (FSG, TSG) and modified (MFSG, MTSG) gums using XRD spectra. Our analysis showed that the XRD spectra of natural FSG and TSG exhibited a highly uneven surface compared to the modified natural gums, which showed the presence of pores and crevices, as illustrated in Figures 8 and 9.

FTIR study

The Fourier transform infrared (FTIR) spectroscopy was used to analyze the chemical properties of the drug nifedipine (NFD). The spectra obtained showed specific peaks at various wavenumbers, namely 3324.66 cm-1, 2950.17 cm-1, 1640.71-1680.74 cm-1, 1491.63-1432.48 cm-1, 1224.27 cm-1, 1189.74-1112.80 cm-1, 1051.66-1021.71 cm-1, and 958.25 cm-1, which corresponded to the presence of aromatic CH stretching, NH stretching, tertiary amide, C-H bending, C-O alkyl aryl ether, tertiary alcohol, primary alcohol, and C=C bending alkene, respectively. The FTIR spectra of NFD are depicted in Figure 10.

Compatibility studies between drug and excipients

In this study, infrared spectroscopy was employed to investigate the compatibility of a pure drug (NFD) with various excipients. The FTIR spectra of the pure drug were compared to those of physical mixtures of the drug with excipients to determine the presence of characteristic peaks of the drug nifedipine in the presence of the excipients. The FTIR spectra of the drug with and without excipients were presented in Figure 10-11, respectively. In addition, peaks at other frequencies related to the polymers or excipients, such as TSG, FSG, MTSG, and MFSG, were also investigated. The TSG spectra showed peaks at 3634.44-3617.18 cm-1 (O-H, glucan backbone), 2312.27-2251.68 cm-1 (C=C stretching), 1754.82-1701.58 cm-1 (CH OH stretching vibration), 1577.73-1542.82 cm−1 (CH2 stretching), and 1425.01-1394.02 cm−1 (C-H stretching). The FSG spectra exhibited peaks at 1102.15-1066.59cm-1 (CH stretching vibration), 1024.82-904.06cm-1 (C-O-C ether group). The MTSG spectra displayed peaks at 3556.91-3522.25cm-1 (overlap of N-H stretching band of the amide functional group). Finally, the MFSG spectra demonstrated peaks at 3924.95-3891.99cm-1 (O-H free hydroxyl alcohol), 3859.01-3737.26cm-1 (N-H stretching, OH alcohol), and 1239.25-1143.54 cm-1 (C-O primary alcohol).

The Fourier Transform Infrared (FTIR) spectra of the drug nifedipine (NFD) were analyzed, revealing specific peak patterns at various wavenumbers. These include 3858.75 cm-1 for the secondary hydroxyl group of NFD, 3670.03 cm-1 for the N-H overlap of the amide with O-H of MTSG, 3555.66 cm-1 for the N-H stretching, OH alcohol of MFSG, O-H cm-1 for the glucan backbone of TSG, 3359.77 cm-1 for the aromatic CH of NFD, 3120.28 cm-1 for the phosphonic acid group, 2381.07 cm-1 for the C≡N and C≡C of NFD, 2173.78 cm-1 for the C=C stretching of TSG, 1916.93 cm-1 for the C=O stretching of MFSG, 1790.93 cm-1 for the tertiary amide of NFD, 1681.94-1655 cm-1 for the CH OH stretching vibration of FSG, 1576.73 cm-1 for the CH2 stretching of TSG, 1521.64 cm-1 for the N-O nitro compound of NFD, 1423.99 cm-1 for the OH bending carboxylic acid of MTSG, 1277.67 cm-1 for the C-O alkyl aryl ether of NFD, 1097.50 cm-1 for the primary alcohol of NFD, and 1053 cm-1 for the CH stretching vibration of FSG. The FTIR data of the NFD-mix (nifedipine drug and polymers together) were depicted in Figure 10 and Figure 11, indicating that the functionalities of the drug moiety remained unchanged, including the intensities of the peak. These results suggest that the drug and excipients are compatible with each other, and these excipients can be used in the formulation.

A differential scanning calorimetry (DSC) analysis was conducted to investigate the possible interaction between the drug and gums. The thermograms obtained from the DSC analysis showed that there was no drug interaction with the excipients.

To obtain the DSC curve of the pure drug nifedipine, a DSC analysis was carried out at a heating rate of 1000C/min from 30 to 350 0C in a nitrogen atmosphere with a flow rate of 30mL/min. The obtained thermograms were then analyzed to determine the temperature required to melt the pure substances and the physical mixtures. However, there was no shifting of thermogram from endothermic to exothermic or vice versa observed. Based on the results of the DSC analysis, it can be concluded that there is compatibility between the drug and excipients.

The DSC thermogram of nifedipine drug with excipients was shown in Figure (DSC spectra of PRP, 5.34-5.36) and (DSC spectra of NFD, Figure 12-13, respectively). All the characteristic peaks of the drugs were observed, and the results of Fourier-transform infrared (FTIR) and DSC

analysis showed no chemical interaction between the drugs and excipients.

Evaluation of blends for immediate release layer prepared by wet granulation method

Blends intended for immediate release layer, produced through the wet granulation method, were subjected to evaluation for various characteristics, including the angle of repose, bulk density, tapped density, Carr's index, and Hausner ratio. The obtained results for these parameters were as follows: the angle of repose ranged between 26.33±0.03 degrees, bulk density was 0.569±0.01 g/cm3, tapped density was 0.741±0.02 g/cm3, Carr's index was 23.21±0.02%, and Hausner ratio was 1.30±0.05. These results reflect the properties of the blends, and were found to be within acceptable limits.

Blends for sustained release layer wet granulation method

Blends intended for the sustained release layer of nifedipine, prepared using the wet compression method, were subjected to evaluation for different parameters. These parameters include angle of repose, bulk density, tapped density, Carr's index, and Hausner ratio. The obtained results for these parameters were found to be within a range of angle of repose (θ) 24.18-28.01±0.01, bulk density (g/cm3) 0.592-0.655±0.04, tapped density (g/cm3) 0.698-0.779±0.02, Carr's index (%) 12.34-16.55±0.05, and Hausner ratio 1.15-1.19±0.07, respectively. These results indicate the properties of the blends and confirm that they are within acceptable limits. The bilayer tablets containing nifedipine, prepared through the wet compression method, were also evaluated for various physical parameters, such as hardness, friability, average weight, and drug content. The obtained results are presented in Table 5.

Determination of swelling index of sustained release layer of bilayer tablets

Table 6 and Figure 14 present the swelling profile of various batches of bilayered matrix tablets. The bioadhesive properties of the polymerincorporated in the formulation were found to be dependent on the extent of swelling. The adhesion between the mucosal layer and the polymer occurs immediately after the onset of swelling, but the bond formed is not very strong. The degree of hydration determines the strength of adhesion, which increases until the point of over-hydration, where disentanglement occurs at the polymer/tissue interface, leading to a sudden decrease in adhesive strength. The findings suggest that the swelling index of bilayered matrix tablets is directly proportional to the concentration of natural gum polymers. Among the formulations tested, the highest swelling index was observed for formulations F, E, G, and H, in that order.

***In-vitro* drug release study from nifedipine bilayer tablets prepared wet granulation method**

The present study investigated the *in-vitro* drug release of bilayer tablets of nifedipine prepared through wet granulation method. The cumulative percentage of drug release was measured and recorded in Table 7 and Figure 15. The findings of the study revealed that tamarind and fenugreek gums, at 20% concentration, sustained drug release up to 18 and 16 hours, respectively. At higher gum concentration (i.e., 40%), both tamarind and fenugreek gums sustained drug release up to 20 and 18 hours, respectively. Additionally, modified tamarind seed gum sustained drug release up to 24 hours, while modified fenugreek seed gum sustained drug release up to 20 hours. The marketed formulation was also found to sustain drug release up to 24 hours. The results of the release rate studies are presented in Table 7 and Figure 15. Moreover, the drug release data were subjected to kinetic analysis using the zero-order, first-order, Higuchi Korsmeyer-Peppas, and Hixon-Crowell kinetic studies. The regression analysis indicated that the drug release pattern from the bilayer matrix tablets followed zero-order and first-order kinetics, as evident from the regression coefficient values are shown in Table 8, respectively.

Stability studies

The quality of the manufactured tablets may alter over time under the effect of external conditions such as temperature and humidity, and this was confirmed by the use of accelerated stability testing. This categorization states that the accelerated stability investigation took place in a chamber for 6 months at 25°C/60% RH and 40°C/75% RH. Tables 10 and 11 display the results that were attained.

Conclusion

The results of the study demonstrate that light tamarind and fenugreek seed gum powder exhibit the necessary physicochemical properties required to be utilized as wet granulation excipients. When sustained-release marketed matrix tablets were employed, the release of nifedipine was slowed

down and extended over a period of 24 hours. On the other hand, when bilayer sustained-release matrix tablets were used, the absorption of nifedipine was fast and followed by longer periods of time when natural and modified forms of fenugreek and tamarind seed gum were employed as matrix tablets. The administration of nifedipine in the form of tablets led to longer drug retention in the body. The pharmacokinetic evaluation demonstrated that the release and absorption of nifedipine were slow and prolonged over an extended period in vivo from the bilayer sustained-release matrix tablets, leading to the maintenance of serum concentrations within a narrow range over a prolonged period. The study underscores the complex nature of pharmaceutical formulations and the absence of a one-size-fits-all approach, highlighting the need for evaluating each drug on a case-by-case basis.

Table: 3 Evaluation of nifedipine blends for immediate release by wet granulation method

Parameters	Results
Angle of Repose (θ)	26.70±0.02
Bulk density (g/cm^3)	0.566±0.01
Tapped density (g/cm^3)	0.745±0.03
Carrs index (%)	24±0.01
Hausner ratio	1.31±0.03

Table: 4. Evaluation of blends for sustained release layer by wet granulation method

Parameters	A-TSG	B-FSG	C-MTSG	D-MFSG	E-FSG	F-TSG	G-MFSG	H-MTSG
Angle of repose (θ)	27.7±0.02	26.41±0.01	26.14±0.03	26.04±0.04	27.03±0.05	28.01±0.01	25.37±0.03	24.18±0.02
Bulk density(g/cm^3)	0.611±0.01	0.592±0.07	0.605±0.01	0.611±0.04	0.655±0.04	0.620±0.03	0.653±0.01	0.606±0.04
Tapped density(g/cm^3)	0.723±0.04	0.690±0.02	0.705±0.01	0.703±0.08	0.779±0.02	0.743±0.07	0.745±0.02	0.698±0.05
Carrs index (%)	15.49±0.03	14.20±0.02	14.18±0.04	13.08±0.04	15.91±0.04	16.55±0.05	12.34±.004	13.18±0.02
Hausner ratio	1.18±0.07	1.17±0.03	1.16±0.02	1.15±0.01	1.18±0.01	1.19±0.07	1.14±0.02	1.15±0.01

Table: 5. Evaluation of nifedipine bilayer matrix tablet using wet granulation method

Parameters	A-TSG	B-FSG	C-MTSG	D-MFSG	E-FSG	F-TSG	G-MFSG	H-MTSG
Hardness (Kg/cm^2)	5.8±0.2	3.8±0.1	5.1±.06	4.5±0.2	4.6±0.1	6.2±0.1	5.0±0.3	6±0.1
Friability (%)	0.23±0.04	0.36±0.04	0.37±0.03	0.40±0.03	0.22±0.02	0.21±0.01	0.27±0.02	0.28±0.04
Average weight (mg)	406±0.1	399±0.7	402±0.3	404±0.7	403±0.9	399±0.23	401±0..96	400±0.90
Drug content	96.80±0.3	96.91±0.1	97.55±0.2	98.78±0.5	97.77±0.4	97.88±0.1	98.93±0.2	99.03±0.9

(Mean ± SD, n = 3)

Table: 6. Swelling index of bilayred matrix tablets of nifedipine

Time	A	B	C	D	E	F	G	H
2 hrs	94.11%	79.3%	82.31%	65.7%	109.61%	150.22%	98.23%	99.92%
4 hrs	171.9%	146.4%	121.6%	124.90%	175.3%	276.3%	175.7%	266.3%
6 hrs	192%	160.20%	143.0%	139.3%	243.79%	394.83%	199.1%	232.10%
8 hrs	167%	111.5%	161.6%	102.65%	170.2%	332.05%	156.4%	205.4%

Table: 7. Cumulative % drug released from bilayer matrix tablet of nifedipine prepared by wet granulation method

HRS	A-TSG	B-FSG	C-MTSG	D-MFSG	E-FSG	F-TSG	G-MFSG	H-MTSG	I-MRK
0	0	0	0	0	0	0	0	0	0
1	19.23±0.20	22.13±0.27	39.9±0.36	43.16±0.32	31.00±0.170	18.55±0.210	20.15±50	24.6±0.62	3.08±0.28
2	27.15±0.232	42.46±0.23	42.28±0.57	52.11±0.26	36.72±0.27	20.85±0.470	21.55±0.27	30.17±0.36	8.83±0.67
4	38.30±0.60	56.18±0.37	60.11±0.22	69.75±0.37	44.18±0.21	29.65±0.36	32.5±0.23	37.33±0.18	12.61±0.30
6	53.37±0.81	67.8±0.51	71.80±0.40	80.70±0.35	47.62±0.23	40.35±0.27	40.3±0.41	40.0±0.42	19.39±0.38
8	66.42±0.45	80.41±0.82	84.5±0.41	87.01±0.30	51.1±0.25	48.7±0.38	51.7±0.49	48.7±0.24	22.8±0.11
10	79.54±0.47	89.43±0.80	88.20±0.46	96.09±0.36	62.3±0.34	51.35±0.32	60.17±0.30	55.15±0.50	26.80±0.41
12	84.28±0.46	94.62±0.23	96.36±0.24	98.78±0.39	70.45±0.400	60.05±0.29	65.85±0.48	63.85±0.47	47.5±0.70
14	96.26±0.53	97.83±0.44	98.40±0.19	98.78±0.39	89.07±0.90	70.4±0.36	71.4±0.41	70.0±0.10	59.3±0.20
16	97.37±0.66	97.83±0.44	99.32±0.63		96.7±0.38	85.85±0.47	78.90±0.81	86.57±0.43	72.9±0.53
17	98.28±0.58		99.32±0.63		98.53±0.60	87.04±0.40	89.05±0.48	92.5±0.46	80.15±0.57
18	98.28±0.58				98.53±0.60	92.13±0.46	96.02±0.20	94.6±0.36	86.73±0.29
19						98.81±0.45	98.93±0.19	96.51±0.25	90.35±0.72
20						98.81±0.45	98.93±0.19	98.41±0.20	93.6±0.20
22								99.34±0.33	96.55±0.38
24								99.34±0.33	97.13±0.20

Table: 8 *In-vitro* drug release kinetic studies of nifedipine from sustained release bilayer matrix tablets prepared by wet granulation method

Batches	Zero-order	First-order	Higuchi	Korsmeyer-Peppas	Hixson-Crowell
Regression values	R_0	R_1	R_H	R_K	R_H
A	0.939	0.952	0.774	0.988	0.981
B	0.849	0.967	0.699	0.985	0.993
C	0.824	0.962	0.694	0.978	0.989
D	0.715	0.894	0.646	0.928	0.903
E	0.905	0.937	0.700	0.971	0.952
F	0.970	0.889	0.807	0.953	0.940
G	0.961	0.993	0.799	0.987	0.994
H	0.936	0.991	0.757	0.990	0.979
I	0.933	0.847	0.928	0.778	0.881

Table: 9. Stability studies of nifedipine bilayer tablets using wet granulation method optimized batches

S. No.	Stability parameter	At 25°C/60% RH			At 40°C/75% RH		
		Initial	3 month	6 month	Initial	3 month	6 month
1	Drug content	97.9±1.2	97.5±1.1	96.8±0.2	97.85±1.5	97.1±0.3	96.6±1.5
2	Hardness	5.2±0.1	4.9±0.5	4.5±0.5	5.1±1.5	4.8±0.5	4.1±0.2
3	Friability	0.37±0.4	0.45±0.5	0.54±0.5	0.42±0.5	0.48±0.2	0.59±0.5

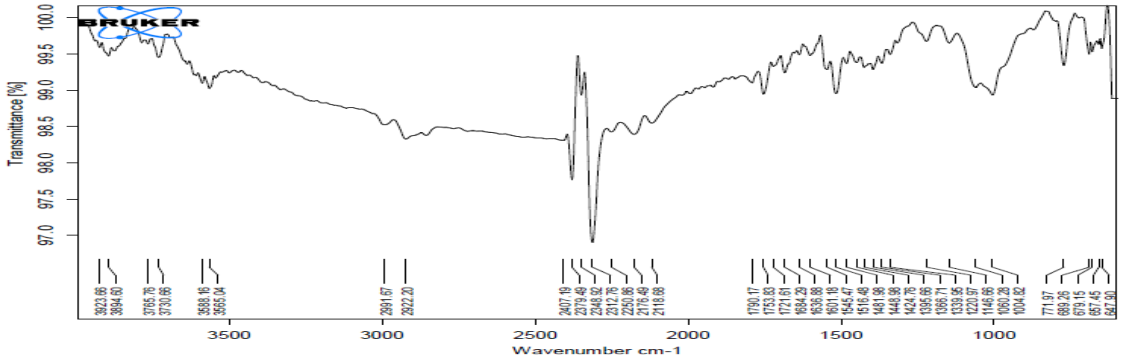

Figure: 1 FTIR spectra of FSG

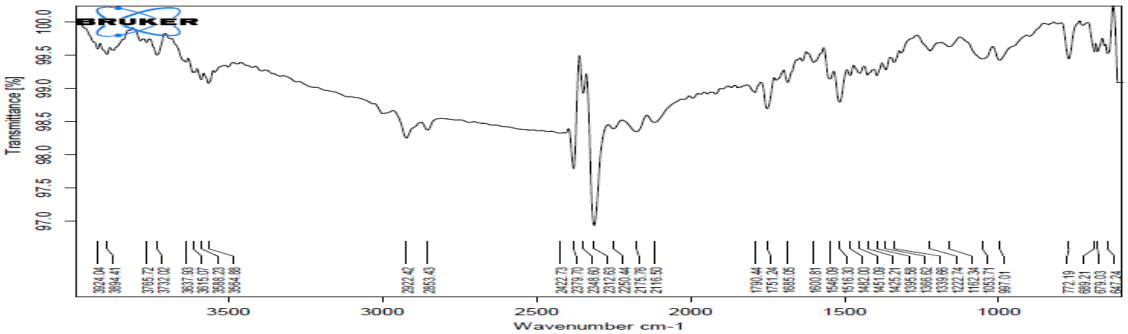

Figure: 2 FTIR spectra of TSG

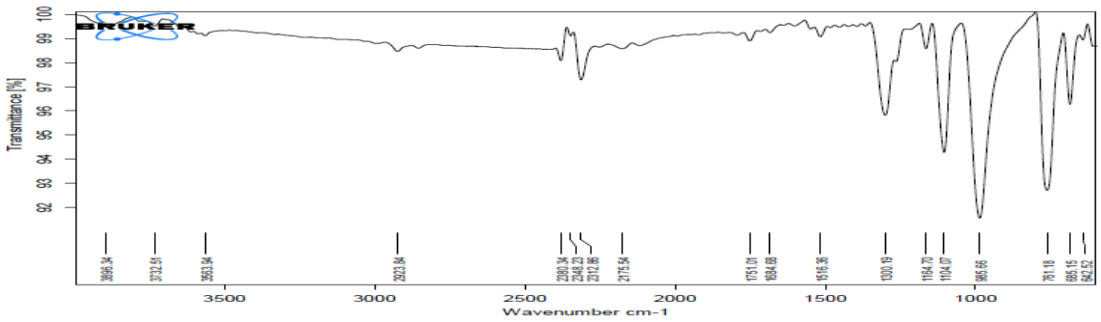

Figure: 3 FTIR spectra of STMP

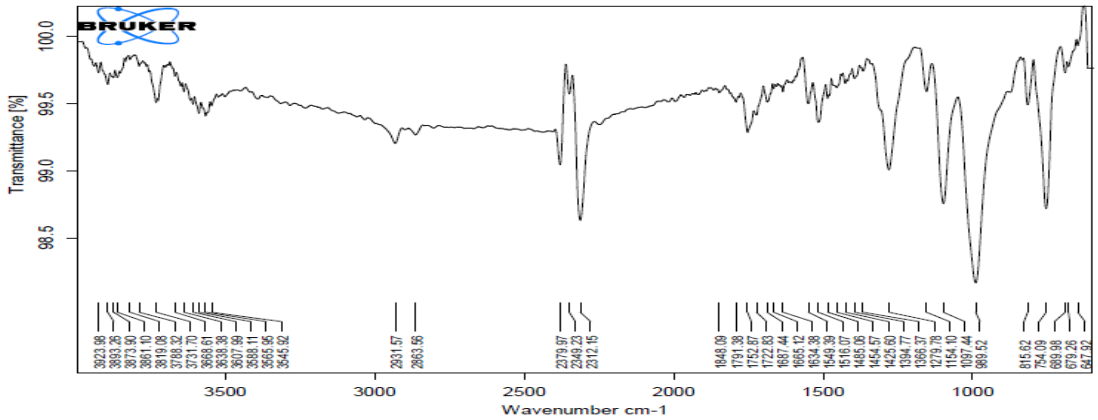

Figure:4 FTIR spectra of modified fenugreek seed gum (MFSG)

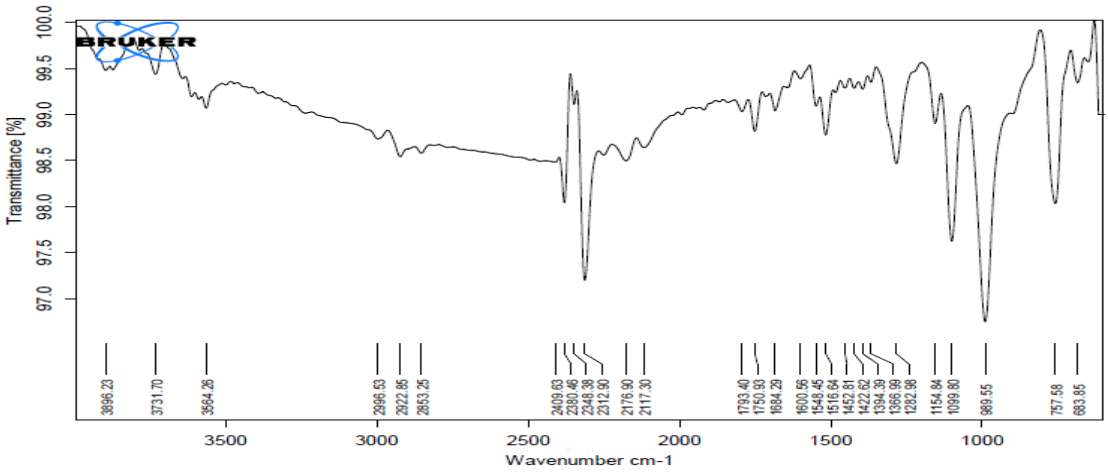

Figure: 5 FTIR spectra of modified tamarind seed gum (MTSG)

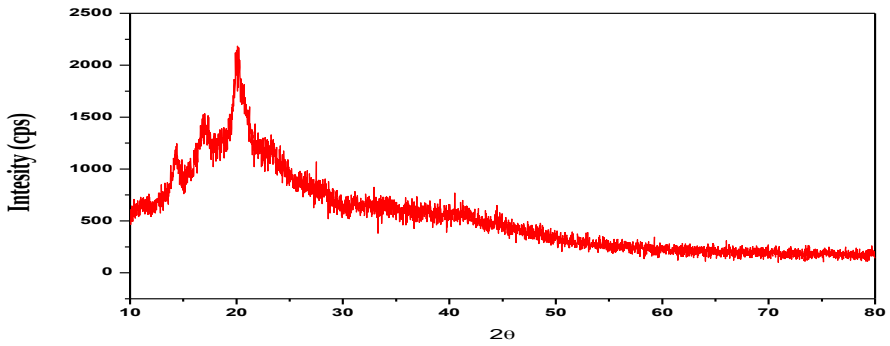

Figure: 6 XRD spectra of fenugreek seed gum (FSG)

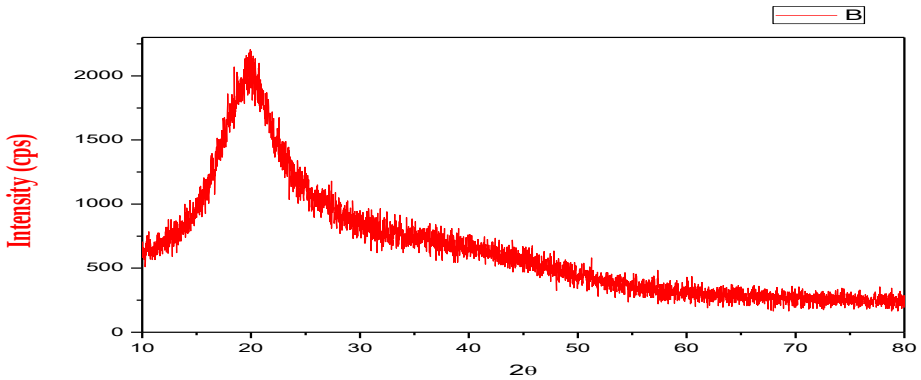

Figure: 7. XRD spectra of tamarind seed gum (TSG)

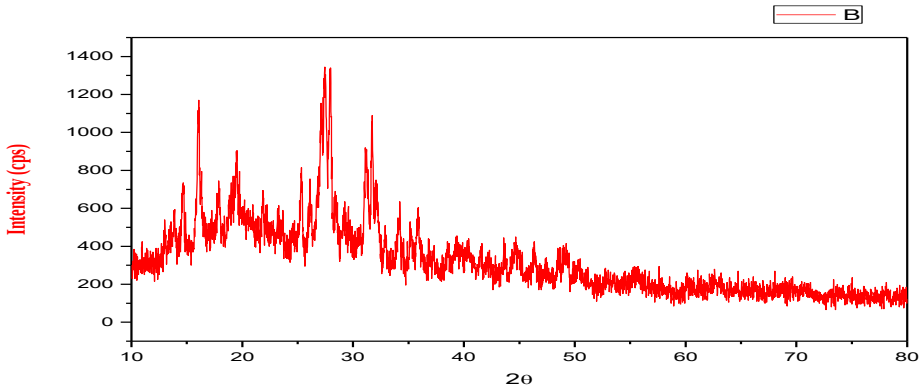

Figure: 8 XRD spectra of modified fenugreek seed gum (MFSG)

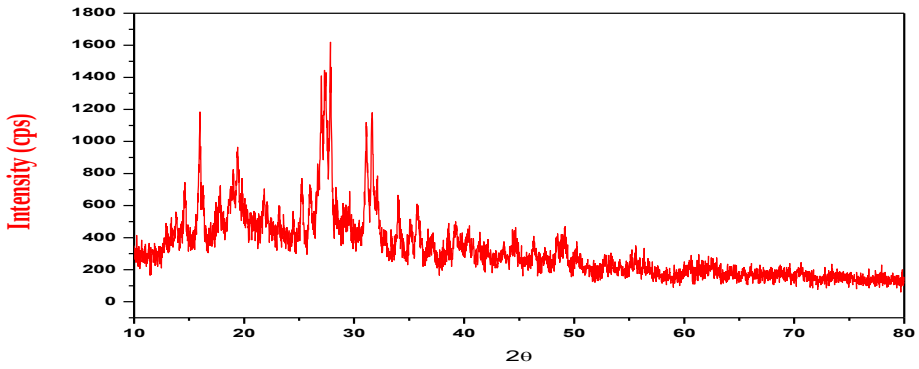

Figure: 9 XRD spectra of modified tamarind seed gum (MTSG)

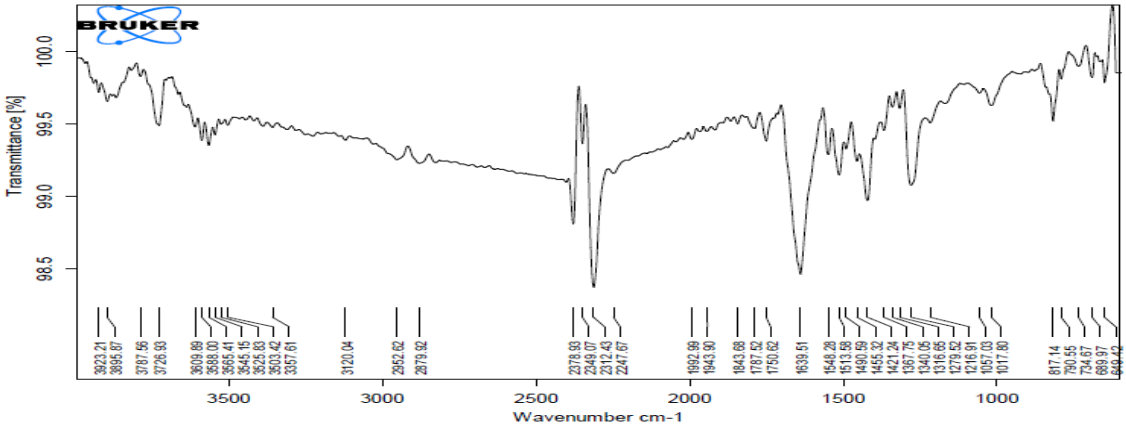

Figure: 10.FTIR spectra of nifedipine pure

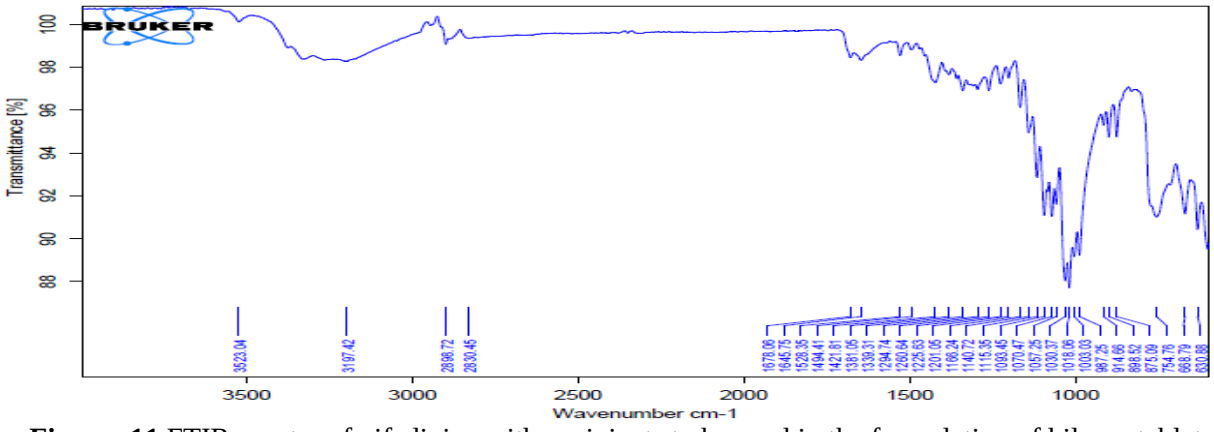

Figure: 11 FTIR spectra of nifedipine with excipients to be used in the formulation of bilayer tablets

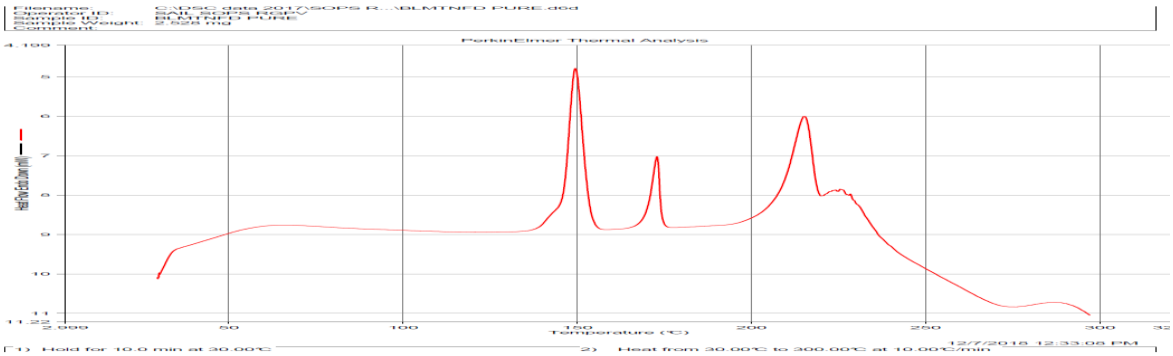

Figure: 12 DSC spectra of nifedipine pure

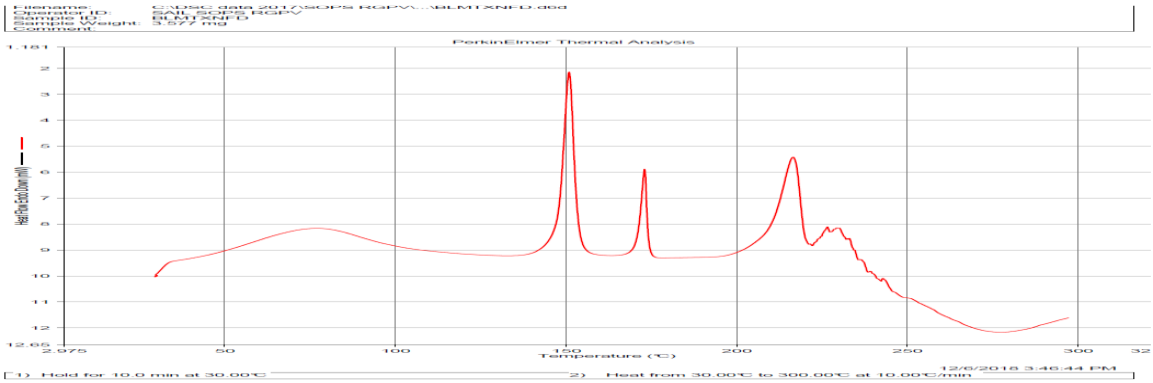

Figure: 13 DSC spectra for nifedipine drug and excipient to be used in formulation of bilayer tablets

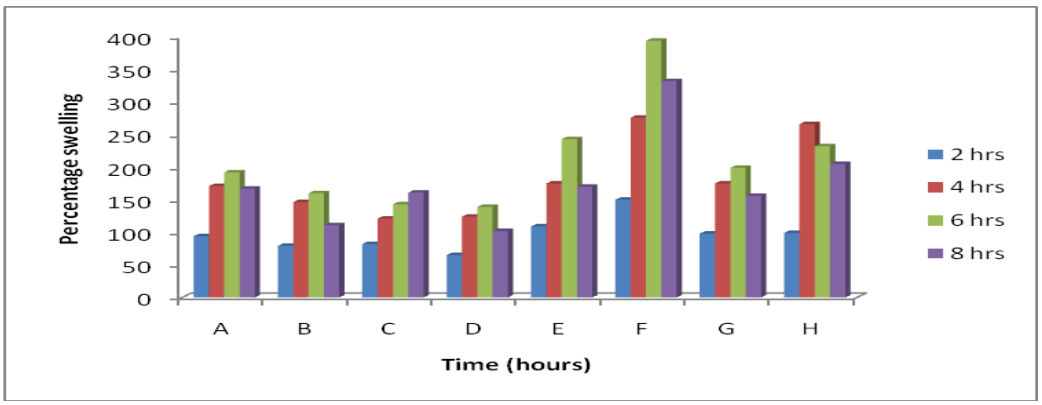

Figure: 14 % Swelling index of bilayer matrix tablet of nifedipine

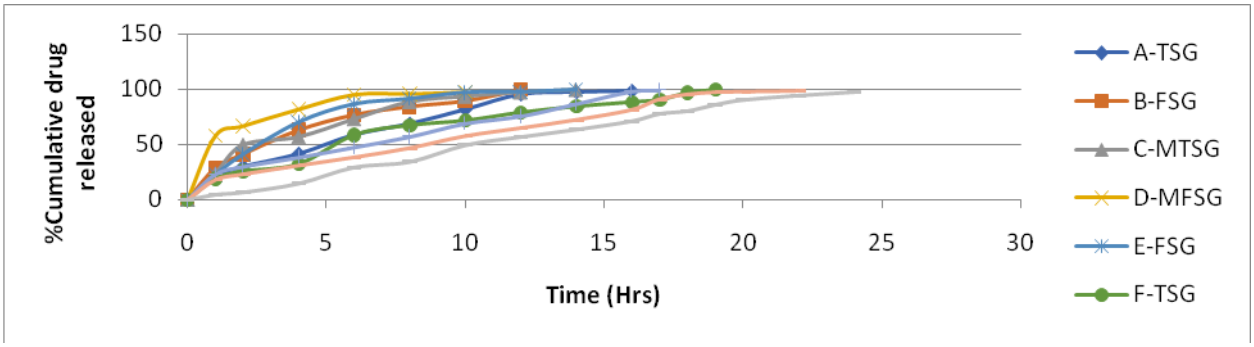

Figure: 15 Cumulative % drug released from bilayer sustained release tablets of Nifedipine prepared by wet granulation method

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