Formulation Development And Evaluation Of Aegle Marmelos Polysaccharide As a Matrix Former

Aishwarya Patil (✉ aishwarya06patil@gmail.com)  
Deepak Gadade  
Balaji Wakure

Research Article

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FORMULATION DEVELOPMENT AND EVALUATION OF AEGLE MARMELOS POLYSACCHARIDE AS A MATRIX FORMER

AISHWARYA. S.PATIL*, DIPAK GADADE,B.S.WAKURE

Authors and Affiliations

Department of pharmaceutics, VDF school of pharmacy, Latur, MH, 413512. India

Contributions

All authors read and approved the final manuscript.

Corresponding author

Correspondence to Aishwarya Shivkumar Patil

Email-aishwarya06patil@gmail.com

ABSTRACT-

Background-
The goal of the whole study was to examine the formulation of tablets containing sustained-release metoprolol succinate employing Aegle marmelose (Bael), a member of the Rutaceae family, as the matrix forming polymer. Excipients play an important function in enhancing a formulation's quality.

Result-The use of aegle marmelose polymers in pharmacy is similar to that of synthetic polymers, which have a wide range of potential applications in innovative drug delivery systems as matrix formers. Due to the fact that these polysaccharide gums are naturally plentiful, biocompatible, biodegradable, and non-immunogenic, and because they boost the economy by giving people access to low-cost formulations made using locally accessible materials. In order to get the desired features of components for drug delivery systems, they can also be altered in a variety of ways, which makes them competitive with the synthetic additives that are now available. The formulation of metoprolol succinate matrix tablets uses the fruits of the Aegle marmelosto as a binder. The metoprolol succinate tablet was created using a 32 factorial design (F1 to F9), and from that F6 batch, tablets were tested for weight variation, hardness, friability, drug content, drug release research, stability study, solubility study, swelling property, and drug excipients compatibility.

Conclusion-
Metoprolol succinate tablets that have been manufactured and tested for stability reveal no major al
iterations, making aegel marmalos polysaccharide a more suitable natural binder than synthetic one.

Additionally, the goal of the study was to determine the potential of natural polysaccharide.

**Keywords:** Aegle marmelos, Metoprolol succinate, matrix former.

**Background:**

Due to a few side effects and the toxicity of synthetic pharmaceuticals, products from natural sources have become an integral part of human medical care. Normal polymers are used in drug stores in a manner that is comparable to that of produced polymers, and they have a broad range of supported discharge definitions. They can also be modified in a variety of ways to provide materials that are specifically designed for drug delivery systems, which allows them to compete with commercially available produced excipients. Different polymers have been investigated as medication-impeding specialties, with each offering a different approach to handling the lattice structure. Given the benefits of the hindering polymer, hydrophilic polymers are the most reasonable for preventing the delivery of medication, and there is growing interest in using these polymers in various applications.

**NATURAL POLYMER APPROACH IN SUSTAINED RELEASE DRUG DELIVERY SYSTEM:**

The use of common polymers and their semi-engineered derivatives in drug delivery is still an active research field. Drug release-restraining polymers are an essential component of network systems. Different polymers have been investigated as drug-impeding experts, each introducing a different approach to handling the framework. Lattice frameworks are often divided into three main groups according on the characteristics of the impeding polymer: hydrophilic, hydrophobic, and plastic. The most effective polymers for preventing drug delivery are hydrophilic ones, and using these polymers to facilitate drug transport is beginning to generate money. Numerous regular polymers have been investigated as specialists in supported discharge, including aloe mucilage, fenugreek mucilage, tamarind gum, okra gum, karaya gum, locust bean gum (LBG), guar gum, and honey beetle venom.

**Plant Description:** A moderately sized, aromatic tree, Bael (Aegle Marmelos (Linn), family Rutaceae, is also known as the Bale organic product tree. The mature organic product mash has a sticky and astringent flavour and is crimson in colour. Carbohydrates, proteins, vitamins C and A, angelenine, marmeline, and dictamine are all present in the mash. The acidic oligosaccharides and the nonpartisan oligosaccharides were represented as 3-0-beta-Dgalactopyranosyl-L-arabinose, 5-0-beta-Dgalactopyranosyl-L-arabinose, and 3-0-beta-Dgalactopyranosyl-D-galactose. Due to their enormous advantages over designed polymers, normal biopolymers have recently spurred scientists to use them more and more. The best materials are polysaccharide gums since they are abundant naturally, biocompatible, biodegradable, and nonimmunogenic.
**Aegle marmelos Gum as Tablet Binder:**
Aegle Marmelos organic product gum was used as a cover to reveal the oral tablet of paracetamol. The wet granulation method was used to prepare the four various tablet designs. The detailing used binder concentrations of 2, 4, 6, and 8% w/w of cordia natural product.

**Purification and standardization of Gum-** (9,10,11,12)

After soaking 250g of A. marmelos edible fruits in double-distilled water, they were cooked for five hours in a water bath till slurry formed.

- To ensure that the majority of the undissolved material settled out, the slurry was chilled and kept in the refrigerator overnight.

- After being decanted off, the upper clear solution was spun at 500 rpm for 20 minutes. At 600C on a water bath, the supernatant was concentrated until the volume was just a third of what it had been initially.

- After being brought to room temperature, the solution was put into three times as much acetone while being continuously stirred.

The precipitate was periodically cleaned with acetone before being vacuum-dried at 50 0C.

- The dried gum was pulverised and kept in a jar with a tight lid for further usage.

**Sustained release dosage forms (SRDF)**

SRDF provides the first distribution of the medication with enough to provide a useful fraction shortly after organisation and then a continual delivery over an extended duration. Supported discharge medication has recently developed into a highly useful tool in clinical practise, providing patients with a variety of real and obvious benefits. By preventing the medication's restorative grouping from changing in the body, it also offers a promising technique for reducing side effects. The majority of prescription medicine delivery systems will continue to be oral aided discharge systems. This product will improve a medication's beneficial effect and security while also improving the patient's comfort.

The basic goal of any medication delivery system is to quickly deliver the correct dosage of medication to the desired place in the body so that it can begin to work and then continue to maintain the desired medication focus. Because they keep the drug concentration in plasma above the minimal compelling fixation and below the minimal harmful level for extended periods of time, these measuring structures are being employed more and more in the treatment of severe and persistent illnesses. As a result, aided drug administration provides flawless medication management with a reduction in dosage repetition and side effects. (18,19,20,21)

**Rationale of sustained release drug delivery**

The essential rule for aided drug administration is to modify medicine release and create a dosing pattern that operates with quiet regularity. It is the most practical measuring method for addressing chronic illness. (19,22,23,25,27)
Mechanism of drug release from matrix tablet

**Ingestion of tablet**

Initial wetting

(Tablet surface wets and hydrophilic polymer begins to hydrate, forming a gel layer. Drug near the surface of the tablet is released)

**Expansion of gel layer**

(Water permeates into the tablet increasing thickness of the gel layer, soluble drug diffuse through the gel layer. Polymer relaxation in the dry core also contributes to dosage swelling.)

**Tablet erosion**

(Outer polymer layer becomes fully hydrated eventually dissolving in the gastric fluid. Water continues to penetrate towards the tablet core)

**Soluble drug**

…”is released primarily by through the gel layer)

**Insoluble drug**

…”is released primarily through diffusion tablet erosion)

Drug release mechanism from SR tablet

**Drug profile**

Metoprolol succinate is a Beta 1-selective (cardio selective) adrenoceptor blocking agent. Its chemical name is \(( I )- (i sopropyl \text{ amino})-3-(p-(2\text{methoxy \text{ethyl}})\text{phenoxy})-2\text{-propanol succinate}\) used for acute myocardial infarction, heart failure, angina pectoris and mild to moderate hypertension. It may also be used for supraventricular and tachyarrhythmias and prophylaxis for migraine headache.

It is soluble in water, soluble in methanol, sparingly soluble in ethanol, slightly soluble in dichloromethane and 2-propanol, practically insoluble in ethyl-acetate, acetone, diethyl ether and heptane.(28,29)
Description

**Name:** Metoprolol succinate

**Structure:**

![Chemical structure of Metoprolol succinate](image)

**Chemical name:**\((\pm)(RS)-1-(\text{Isopropylamino})-3-[4-(2\text{-methoxyethyl})\text{phenoxy}]\) propan-2-ol Succinate

**Molecular formula:** \((C_{15}H_{25}NO_3)\cdot C_4H_6O_4\)

**Molecular weight:** 652.8

**Description:** Metoprolol succinate is a white, bitter, crystalline and odorless solid dispersion.

**Melting Point:** 138 to 142°C

**Solubility:** It is freely soluble in water and ethanol

**pka:** 3-4

**Bioavailability:** 75%

**Half life:** 5-6 hour

Pharmacokinetics

Absorption

Metoprolol succinate is easily absorbed from the gastrointestinal tract and has a linear relationship between the supplied dose and its maximum plasma concentration. Data on urine recovery after oral medicine administration revealed that more than 90% of the oral dose (100 mg) was absorbed.

Distribution

Up to 10 g/ml, metoprolol succinate appears to have a concentration-independent 20% binding affinity for human plasma proteins. Metoprolol succinate has a distribution volume of around 2.7 L/kg.

Metabolism

Metoprolol succinate is metabolised by the cytochrome P450 isozyme CYP2D6 in the liver. 30%
of the dose is removed in the urine as the original medicine, whereas 60% of the dose is excreted as metabolites. The remainder is either eliminated as unidentified metabolites. Phase II hepatic metabolism causes the metabolites to become water-soluble, and they are subsequently removed by the kidneys.

**Elimination**

Metoprolol succinate is broken down by the liver, and the metabolites are primarily eliminated via the kidneys. The mean terminal plasma elimination half-life of racemic metoprolol M1 was 6.3 ± 1.4 hours. Plasma elimination half-life of metoprolol succinate rose from about six to seven hours following multiple doses. (30,31)

**Mechanism of Action**

Heart rate, cardiac output, and contraction force are all decreased by metoprolol succinate. It lengthens systole and prevents the synergy of ventricular fibre contraction by interfering with conduction. On a typical person at rest, the effect is minimal, but it becomes apparent when sympathetic activity is excessive. Cardiovascular work and oxygen consumption similarly decrease as the sum of heart rate and aortic pressure falls. Total coronary flow is decreased in the subepicardial zone, but mostly unaltered in the subendocardial region. The overall effects on angina patients include improvements in oxygen supply or demand status and better exercise tolerance. It enhances the BP rise brought on by adrenaline while suppressing the vasodilatation and BP decline caused by isopropanol. Little to no direct change is observed in BV or BP as a result. (30,31)

**Therapeutic Uses**

To treat high blood pressure, metoprolol succinate is used either alone or in conjunction with other drugs. Additionally, it is used to treat heart attacks and prevent angina. Metoprolol with an extended release (long action) is also prescribed in conjunction with other drugs to treat heart failure.

**Adverse Effects**

Nausea, vomiting, perspiration, and constipation are the most often reported adverse medication responses. Although it is less of an issue than with opioids, drowsiness is mentioned. In normal doses, respiratory depression, a typical adverse effect of the majority of opioids, is not clinically relevant.

**Overdose**

As with other opioid analgesics, miosis, vomiting, circulatory collapse, drowsiness and coma, seizures, and respiratory depression are all signs of overdose. Supportive measures should be put in place, such as maintaining heart function and the patency of the airway; using naloxone to reverse respiratory depression; and using diazepam to control fits.

**Dose**

Adults (17 years of age and over) - 400/day (in divided manner) not to exceed 400 mg.
Analytical method development and validation

Calibration Curve of Metoprolol Succinate

Preparation of stock solution

Using the Shimadzu UV1700, the UV spectrum of metoprolol succinate was measured. A stock solution (1000 g/ml) was created by dissolving an accurately weighed 100 mg of the medication in enough 6.8 phosphate buffer to fill a capacity of 100 ml. To get the concentration of 10 g/ml, 0.1 ml of the aliquot was taken out and volume was increased up to 10 ml using 6.8 phosphate buffer. The resulting solution's spectrum was recorded after being scanned from 200 to 400 nm (figure 5).

Preparation of serial dilution

To prepare a series of concentrations ranging from 10 to 50 g/ml, various aliquots from the stock solution were collected and diluted with distilled water individually. The UV spectra of metoprolol succinate in buffer pH 6.8 was scanned from 200-400 nm, and the maximum wavelength was found to be 223 nm. On a UV-Visible Spectrophotometer, absorbance was measured at 223 nm against a buffer with a pH of 6.8 as a blank (UV-1700 SHIMADZU). The calibration curve was created by graphing the absorbance against the metoprolol succinate concentration.

Analytical method validation

The developed method was validated according to ICH Guidelines

Accuracy

To ensure the accuracy, known amounts of pure drug were added to the solvent and these samples were reanalyzed by the proposed method and also % recovery was determined.

Precision

Pure drug solution (within the working limits) was evaluated and repeated six times to assess the method's repeatability. Intra-day and inter-day fluctuation studies further provided proof of the method's accuracy. In intra-day experiments, the percentage RSD was computed after three iterations of measurements of the standard and sample solutions. In inter-day experiments, standard and sample solution concentrations were measured three times on three separate days, and the % RSD was computed. The relative standard deviation (%) was less than 2.0, which shows that the proposed method has a high degree of precision. (36,37)

Linearity and Range

Aliquots of the stock solution of Metoprolol Succinate (0.5-3 ml of 100μg/ml) were transferred into 10 ml standard flasks and made volume using phosphate buffer (pH-6.8). The absorbances of the solutions of different concentrations were measured at 223 nm against phosphate buffer (pH-6.8) as blank. Linearity was observed between 5-30μg/ml

Limit of detection (LOD)

LOD was calculated from the formula
DL = 3.3 I/S

Where, I is intercept and S is slope of calibration curve.

**Limit of quantification (LOQ)**

LOQ is calculated from formula

\[ QL = \frac{10 \cdot I}{S} \]

Where, I is intercept and S is slope of calibration curve

**Solubility:**

The compound's solubility was tested in water, 0.1 N HCl, and phosphate buffer at pH 6.8. In 5 ml of solvent, the extra medication was dissolved. After that, the solution was ultrasonically treated for 30 minutes. After that, it was let to stand for 24 hours at room temperature in securely covered vials in order to reach saturation equilibrium. The solution was run through Whatman filter paper No. 41 after 24 hours. It was then properly diluted with the solvent before being analysed by UV Spectrophotometry at 223nm (36,37)

**Drug excipient compatibility study**

For the successful creation of a suitable and effective solid dosage form, meticulous excipient selection is paramount. Excipients are added to medications to boost their bioavailability, regular release, and convenience of administration. Excipients’ compatibility with medications needs to be investigated. Heat analysis and IR spectroscopy were employed to investigate and predict probable physicochemical interactions between components in a formulation as well as to select compatible excipients.

**Physical Compatibility**

The physical mixture of the pure medication and polymers in the ratio of 1:1 was used to study the compatibility of the excipients. The mixes were made by triturating the medication with polymers, and they were kept in closed vials at 121°C for 15 minutes. In closed and open vials, at room temperature and 40% relative humidity, for 4 weeks. (Table No.14)

**Chemical Compatibility - Differential Scanning Calorimeter (DSC)**

A differential scanning calorimeter (DSC) measures the heat gain or loss brought on by physical or chemical changes within a sample as a function of temperature. Quantitative measurement of these processes is used in many preformulation investigations, including those on purity, polymorphism, solvation, degradation, and excipient compatibility. Drugs and drug-polymer combinations were tested using differential scanning calorimetry (DSC). The physical mixtures of pharmaceuticals and polymers were created for compatibility testing by triturating the medications and polymers (1:1) in a dried mortar for 5 minutes. After then, the combinations were kept there for 24 hours. The samples were sealed in aluminium pans with the medicine and polymer combination after being weighed at a range of 2 to 5 mg (1:1:1). The sealed aluminium
pan was heated at a rate of 10°C/min over a temperature range.

**Formulation study**

**Preliminary trial batches**

Composition of preliminary trials batches for sustained release formulation is shown in Table 2. In all the formulations dose of metoprolol succinate 50mg was taken. Metoprolol succinate matrix tablets were prepared by wet granulation method the excipients used were spray dried lactose as a filler, Aegle marmelos as a matrix former, PVP K30 (granulating agent), magnesium stearate (lubricating agent) and talc (glident). Sustained release matrix tablets were prepared by wet granulation method. All the ingredients was passes through sieve # 100, weight accurately, mixed and granulated using PVP K-30 in isopropyl alcohol as granulating aid. The granules obtained were dried in oven at 50°C for 2 hours. After drying, granules passed through sieve # 16 to obtained uniform size. (36,37)

<table>
<thead>
<tr>
<th>ingredients</th>
<th>P1(mg)</th>
<th>P2(mg)</th>
<th>P3(mg)</th>
<th>P4(mg)</th>
<th>P5(mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metoprolol succinate</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Spray dried lactose</td>
<td>181.5</td>
<td>179</td>
<td>176.5</td>
<td>173.5</td>
<td>169</td>
</tr>
<tr>
<td>Aegle marmelos</td>
<td>7.5</td>
<td>10</td>
<td>12.5</td>
<td>15.5</td>
<td>20</td>
</tr>
<tr>
<td>PVP K30</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Mg.stearate</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>talc</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Total weight</td>
<td>250</td>
<td>250</td>
<td>250</td>
<td>250</td>
<td>250</td>
</tr>
</tbody>
</table>

**Table 2: Translation of coded values for 3² factorial experimental designs**

<table>
<thead>
<tr>
<th>Sr. No</th>
<th>Coded Value</th>
<th>Experimental Level</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Actual Value</td>
</tr>
</tbody>
</table>
Composition of final optimized batches for sustained release formulation is shown in Table 4. Aegle marmalos and PVP K30 were used in 2 to 8% and 0.5 to 5% as sustained release polymer respectively. In the present study, $3^2$ full factorial design was employed containing 3 factors evaluated at 2 levels and experimental trials were performed at all 9 possible combinations. The independent variables selected for the present study was PVP K30(X1), Aegle marmalos(X2). The translation of coded values for $3^2$ factorial experimental designs is shown in Table 4.

**Formulation of Metoprolol succinate SR matrix tablets**

**Table 3: Formulation of 3²Factorial Design Batches**

<table>
<thead>
<tr>
<th>Ingredient(mg)</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
<th>F7</th>
<th>F8</th>
<th>F9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metoprolol succinate</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Spray dried lactose</td>
<td>186.5</td>
<td>176.5</td>
<td>179</td>
<td>181.5</td>
<td>174</td>
<td>166.5</td>
<td>169</td>
<td>171.5</td>
<td>161.5</td>
</tr>
<tr>
<td>Aegle marmalos</td>
<td>5</td>
<td>5</td>
<td>12.5</td>
<td>5</td>
<td>12.5</td>
<td>20</td>
<td>12.5</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>PVP K30</td>
<td>2.5</td>
<td>12.5</td>
<td>2.5</td>
<td>7.5</td>
<td>7.5</td>
<td>7.5</td>
<td>12.5</td>
<td>2.5</td>
<td>12.5</td>
</tr>
<tr>
<td>Mg. Stearate</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Talc</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>250</td>
<td>250</td>
<td>250</td>
<td>250</td>
<td>250</td>
<td>250</td>
<td>250</td>
<td>250</td>
<td>250</td>
</tr>
</tbody>
</table>
Evaluation of Metoprolol Succinate (SR) matrix tablets

Appearance

The thickness of tablet as a dimensional variable was evaluated. The tablet thickness was controlled within ±5% of average value by Vernire calliper. The colour, odour and any other flaws like chips, cracks, surface texture, etc. are other important morphological characteristics were observed.

Weight variation test

Twenty tablets were taken and average weight of the tablet was determined. The tablets were weighed individually and the weight variation was determined.

Hardness

Tablet hardness is defined as force required to crushing the tablet in diametric compression test. The hardness was measured with Monsanto hardness tester. The tablets were placed diametrically between two plungers and the lower plunger is kept in contact of tablet to read as zero. The upper plunger is forced against a spring by turning the screw until tablet fractures.

Friability

Twenty tablets were weighed and subjected to friability test in Roche friabilator. The pre-weighed sample was placed in friabilator which revolves at 25 rpm for 4 min. dropping the tablets through a distance of 6 inch with each revolution. This process was repeated for all formulations and the percentage friability was calculated.

Drug content

Randomly selected 1 tablet from each batch was crushed in a mortar and pestle. The crushed powder equivalent to 25 mg of metoprolol succinate was taken and dissolved in 25 ml of buffer pH 6.8 (1000µg). Then filtered through Whatman filter paper 0.45micron. The concentration of metoprolol succinate was determined by measuring the absorbance at 223nm.(38)

Drug Release Study

Utilizing USP apparatus type II, the drug release rate from metoprolol succinate matrix tablets (n=3) was calculated (Labindia, India). Using 500 ml of 6.8 phosphate buffer, the dissolving test was run for 20 hours at 37 0.5 C and 50 rpm. At certain intervals, a sample (5 ml) was removed and
replaced with brand-new dissolving medium of the same volume. The samples were run through a 0.45 micron Whatman filter paper. The solutions' absorbance was determined at 274 nm. The following tables provide information on the cumulative drug release of the sustained release metoprolol succinate matrix tablet. The Table displays the medication release profiles for factorial batches. (44)

**Table 4: Dissolution limit as per USP**

<table>
<thead>
<tr>
<th>Time (hrs)</th>
<th>% cumulative drug release</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Not more than 25%</td>
</tr>
<tr>
<td>4</td>
<td>Bet 20-40%</td>
</tr>
<tr>
<td>8</td>
<td>Between 40-60%</td>
</tr>
<tr>
<td>20</td>
<td>Above 80 %</td>
</tr>
</tbody>
</table>

**Differential Scanning Calorimetry (DSC)**

The thermal behavior of metoprolol succinate was studied using Shimadzu DSC TA60 WS Thermal Analyzer. Accurately weighed samples of (6.06 mg) were hermetically sealed in aluminium pan and heated at a constant rate of 20°C/min over temperature range of 100 to 300°C. The DSC thermogram was recorded.

**Determination of Flow Properties of Drug and Polymer**

The quality of tablet depends upon the quality of powder from which it is prepared. Therefore, it is quite necessary to evaluate the powder and see whether it is of required quality or not. The powder of factorial batches were evaluated for Bulk density, Tapped density, Carr’ index (compressibility), Angle of repose and Hausner’s ratio. The evaluated parameters of powder are reported in the table.
Physicochemical properties of aegle marmalose

Loss on drying:

The 5 gm gum was dried at 105 ± 5 °C till the constant weight of gum was obtained. The loss on drying was found to be less than 8 % w/w

Ash value:

1gm of gum was accurately weighed and evenly distributed it in the crucible. It was dried at 105 °C for one hour and ignited in muffle furnace at 600 ± 25 °C. Percentage of ash content was found to be less than 7 % w/w.

Swelling property of aegle marmalos

The fruits of A. marmelos is nontoxic. 250 mg of A.marmelos gum was allowed to hydrate in 25ml of distilled water at 25°C in a 25 ml graduated cylinder and volume measured at 5 min. intervals until there was no further hydration observed. The swelling property was determined at different time intervals (Table

Stability studies

The stability study of the selected optimized F6(Tablet) formulations was carried out according to ICH guidelines at, accelerated 40°C Cand room temperature condition,25°C ± 2°C/60% ± 5% RH % and room temperature for three month by storing the samples in stability chamber (Table 26 and 27) (40,44)

In vitro drug release study

Using USP apparatus type I, the drug release rate from metopropol succinate SR matrix tablets (n=3) was calculated (Labindia, India). Using 500 ml of buffer with a pH of 6.8, the dissolving test was run for 20 hours at 37 0.5 C and 50 rpm. At certain intervals, a sample (5 ml) was removed and replaced with brand-new dissolving medium of the same volume. A Whatman filter paper was used to filter the samples. The solutions' absorbance was determined at 274 nm using a UV-visible spectrophotometer (UV-1700 SHIMADZU). Using PCP Disso ver. 3.0, the drug release and drug release kinetics were determined. In Tables 19 and the drug release profiles of factorial batches, the cumulative drug release of all 9 batches is presented.

Result -

Metoprolol succinate obtained for the study was recognised, and its purity was evaluated. Melting point, UV, IR, and differential scanning colorimetry were used to identify the material. Metoprolol succinate Sustained Release Matrix Tablet Formulation and Development Using Natural Polysaccharide

Melting point

The average melting point of Metoprolol succinate was determined by capillary method and was found to be138°C, which is in good agreement with reported melting point.

Stability studies
The stability study of the selected optimized F6(Tablet) formulations was carried out according to ICH guidelines at, accelerated 40°C and room temperature condition, 25°C ± 2°C/60% ± 5% RH % and room temperature for three month by stored the samples in stability chamber (Table 26 and 27).

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**UV Spectra**

The UV spectrum of Metoprolol succinate solution (50µg/ml) exhibited wavelength of absorbance maximum at 223 nm which complies with the reported.

![Figure 1: UV spectra of metoprolol succinate](image-url)
DSC Spectra

DSC thermogram of Metoprolol succinate showed one endothermic peak of fusion, having peak maximum of 139.93°C. This was in accordance with the reported. (Figure 7 On the basis of melting point, UV spectrum, Infrared spectrum and DSC thermogram the procured sample of Metoprolol succinate was found to be of acceptable purity and quality. The sample was taken for further studies.

![DSC Thermogram of Metoprolol Succinate](image)

Figure 2: DSC Thermogram of metoprolol succinate

Drug and Polymer flow properties

Table 5. Determination of Flow Properties of Drug and Polymer

<table>
<thead>
<tr>
<th>Drug/Polymer</th>
<th>Bulk Density (gm/cm³)</th>
<th>Tapped Density (gm/cm³)</th>
<th>Carrs Index (%)</th>
<th>Hausner Ratio</th>
<th>Angle of Repose (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metoprolol succinate</td>
<td>0.475</td>
<td>0.53</td>
<td>11.3209</td>
<td>1.3213</td>
<td>29.79</td>
</tr>
<tr>
<td>Aegle marmelos</td>
<td>0.435</td>
<td>0.57</td>
<td>10.96%</td>
<td>1.33</td>
<td>31.12</td>
</tr>
<tr>
<td>PVP K30</td>
<td>0.481</td>
<td>0.56</td>
<td>14.31</td>
<td>1.21</td>
<td>27.32</td>
</tr>
</tbody>
</table>
Angle of repose is the most pertinent angular property among those that have been used to evaluate flowability. Investigated was the granules' angle of repose. After the lubricant was added, the Angle of repose (°) value fell. An indicator of powder flowability from the hopper to the die chamber is the angle of repose (°). All of the formulations' angles of repose fell between 20 and 30 degrees, indicating adequate flowability.

Based on the size, shape, and propensity of particles to stick together, bulk density can affect a number of qualities, including compressibility, tablet porosity, dissolving, and other features. Granules were discovered to have a bulk density of 0.46 to 0.48 gm/cm³. The results show that the granules have an excellent packing capacity.

Granules from different batches were found to have tap densities between 0.5 and 0.56 g/cm³. The % compressibility of the granules was calculated using the bulk density and tap density.

The granules' Carr's index was found to be in the range of 11.11 to 16.5, showing good compressibility.

The Hausner's ratio values were found to be between 1.11 to 1.19, indicating good flowability.

The tap densities of the granules of batches were found in the range of 0.53-0.56 gm/ cm³. The bulk density and tap density was used to calculate the percent compressibility of the granules.

The Carr’s index of the granules was observed in range of 11.11 to 16.5, indicating good compressibility of the granules.

The values of the Hausner’s ratio were found to be in the range of 1.11 to 1.19 indicating good flowability.

**physicochemical properties of aegle marmelos**

**Table 6: Physicochemical properties of aegle marmelos**

<table>
<thead>
<tr>
<th>SPECIFIED TEST</th>
<th>RESULT</th>
<th>SPECIFICATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Description</td>
<td>Brown coloured dry powder</td>
<td>Brown coloured dry powder</td>
</tr>
<tr>
<td>Solubility in water</td>
<td>72.18%</td>
<td>NLT 70%</td>
</tr>
<tr>
<td>Loss on drying</td>
<td>2.02%</td>
<td>NMT 7.0%</td>
</tr>
<tr>
<td>Ash value</td>
<td>8% w/w</td>
<td>NLT 7% w/w</td>
</tr>
<tr>
<td>pH of 1% solution</td>
<td>4.87</td>
<td>4-7</td>
</tr>
</tbody>
</table>
Table 7: Swelling property of Aegle marmelos

<table>
<thead>
<tr>
<th>Natural gum</th>
<th>After 5 min (ml)</th>
<th>After 10 min (ml)</th>
<th>After 15 min (ml)</th>
<th>After 20 min (ml)</th>
<th>After 30 min (ml)</th>
<th>After 35 min (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aegle marmelos</td>
<td>0.5</td>
<td>0.7</td>
<td>0.9</td>
<td>1.1</td>
<td>1.3</td>
<td>1.3</td>
</tr>
</tbody>
</table>

Solubility

Table 8: The solubility of Metoprolol succinate in various medium is shown in following table

<table>
<thead>
<tr>
<th>Sr. no.</th>
<th>Medium</th>
<th>Solubility (mg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Water</td>
<td>12.8</td>
</tr>
<tr>
<td>2.</td>
<td>0.1 N HCl</td>
<td>21.5</td>
</tr>
<tr>
<td>3.</td>
<td>Methanol</td>
<td>99.25</td>
</tr>
<tr>
<td>4.</td>
<td>Phosphate buffer</td>
<td>35.5</td>
</tr>
<tr>
<td></td>
<td>pH 6.8</td>
<td></td>
</tr>
</tbody>
</table>

Analytical method development and validation

Analytical Method Development

The UV spectrophotometric method was selected for estimation of Metoprolol succinate. The UV spectrum exhibited maximum absorbance (λmax) at 223nm. The standard calibration curve exhibited good coefficient of correlation as shown in Table 8

Table 9: calibration curve in phosphate buffer 6.8

<table>
<thead>
<tr>
<th>CONC(μg/ml)</th>
<th>ABSORBANCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>0.134</td>
</tr>
<tr>
<td>10</td>
<td>0.258</td>
</tr>
<tr>
<td>15</td>
<td>0.366</td>
</tr>
<tr>
<td>20</td>
<td>0.479</td>
</tr>
</tbody>
</table>
Figure 3: Calibration curve of metoprolol succinate in 6.8 phosphate buffer

Analytical method validation

Developed method was validated and validation parameters are listed in Table 7

Table 10: Validation Parameter

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Limit</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accuracy</td>
<td>98 - 102</td>
<td>99.03</td>
</tr>
<tr>
<td>Repeatability</td>
<td>%RSD &lt; 2</td>
<td>0.0881%</td>
</tr>
<tr>
<td>Intraday precision</td>
<td>%RSD &lt; 2</td>
<td>1.13561</td>
</tr>
</tbody>
</table>
Inter day precision %RSD < 2 1.1551

Linearity and R2 > 0.9997 0.999
Range %RSD < 2 5-25(μg/ml)
LOD - 0.7671(μg/ml)
LOQ - 2.3248(μg/ml)

From the above observation it was revealed that the analytical method complies with the validation parameters.

Drug excipients compatibility

Physical Compatibility
In all physical mixtures of drug and polymer, there was no physical change observed.

Table 11: Shows Excipient Compatibility Study

<table>
<thead>
<tr>
<th>Sr No</th>
<th>Conditions</th>
<th>Time</th>
<th>Open\Closed</th>
<th>Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>121° C</td>
<td>15 min</td>
<td>closed</td>
<td>No Colour change</td>
</tr>
<tr>
<td>2</td>
<td>Room temp</td>
<td>4 weeks</td>
<td>closed\open</td>
<td>No Colour change</td>
</tr>
<tr>
<td>3</td>
<td>Refrigerator</td>
<td>4 weeks</td>
<td>Closed\open</td>
<td>No Colour change</td>
</tr>
<tr>
<td>4</td>
<td>40° C/75%RH</td>
<td>4 weeks</td>
<td>open No</td>
<td>No Colour change</td>
</tr>
</tbody>
</table>
Chemical compatibility

DSC Studies

Figure 4. DSC Thermogram of Physical Mixture of aegle marmelos

Figure 5: DSC Thermogram of Physical Mixture of metoprolol succinate + aegle marmalos
The endothermic peak at 145.90ºC can be attributed as melting point of Metoprolol succinate. The thermogram showed that the Metoprolol succinate and aegle marmelos compatible with each other.(fig. 10)

FORMULATION STUDIES
Preliminary Trial Batchs
Results showed that the drug release increases with increase in the concentration of aegle marmelos gum.

Table 12: Dissolution of Preliminary Trial Batches

<table>
<thead>
<tr>
<th>time</th>
<th>P1</th>
<th>P2</th>
<th>P3</th>
<th>P4</th>
<th>P5</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10.58</td>
<td>7.731</td>
<td>14.97</td>
<td>16.71</td>
<td>15.324</td>
</tr>
<tr>
<td>4</td>
<td>24.41</td>
<td>25.63</td>
<td>32.77</td>
<td>35.87</td>
<td>34.270</td>
</tr>
<tr>
<td>8</td>
<td>43.24</td>
<td>45.62</td>
<td>51.71</td>
<td>58.54</td>
<td>56.94</td>
</tr>
<tr>
<td>20</td>
<td>70.51</td>
<td>75.33</td>
<td>81.11</td>
<td>85.46</td>
<td>85.95</td>
</tr>
</tbody>
</table>
DISSOLUTION PROFILE

Figure 6: % cumulative drug release of primary batches

The release profile of preliminary formulations (p1 to p5 given in Table 15. Formulation p1 to p2 releases 70.5, 75.33% drug release in 20h respectively, which is not acceptable with normal range. Formulation p3, p4 and p5 shows 81.11%, 85.46%, 85.95% drug release within 20 hr respectively, which is acceptable range.
Formulation of final optimized SR matrix tablet

Table 13: Final optimized batches

<table>
<thead>
<tr>
<th>TIME</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
<th>F7</th>
<th>F8</th>
<th>F9</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>32.76</td>
<td>40.790</td>
<td>56.18</td>
<td>42.059</td>
<td>59.393</td>
<td>58.741</td>
<td>48.13</td>
<td>41.162</td>
<td>41.10</td>
</tr>
<tr>
<td>20</td>
<td>65.94</td>
<td>67.84</td>
<td>86.253</td>
<td>71.199</td>
<td>92.154</td>
<td>95.633</td>
<td>91.33</td>
<td>87.397</td>
<td>80.58</td>
</tr>
</tbody>
</table>

Figure 7: % cumulative drug release of final batches
## Evaluation of Metoprolol succinate (SR) Tablets

### Table 14: Evaluation parameters of final batches

<table>
<thead>
<tr>
<th>Batch</th>
<th>Appearance</th>
<th>Weight variation (mg ± SD)</th>
<th>Hardness (Kg/cm²) ±SD</th>
<th>Friability% ±SD</th>
<th>Thickness (mm) ±SD</th>
<th>% Drug Content ±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>Brownish Circular 10mm</td>
<td>249±0.47</td>
<td>6.3±0.28</td>
<td>0.61±0.02</td>
<td>3.18±0.12</td>
<td>65.94%</td>
</tr>
<tr>
<td>F2</td>
<td>Brownish Circular 10mm</td>
<td>250±0.81</td>
<td>6.1±0.5</td>
<td>0.71±0.04</td>
<td>3.20±0.22</td>
<td>67.84%</td>
</tr>
<tr>
<td>F3</td>
<td>Brownish Circular 10mm</td>
<td>250±1.69</td>
<td>6.7±0.31</td>
<td>0.65±0.09</td>
<td>3.18±0.03</td>
<td>86.24%</td>
</tr>
<tr>
<td>F4</td>
<td>Brownish Circular 10mm</td>
<td>250±1.24</td>
<td>6.3±0.21</td>
<td>0.52±0.03</td>
<td>3.20±0.13</td>
<td>71.2%</td>
</tr>
<tr>
<td>F5</td>
<td>Brownish Circular 10mm</td>
<td>250±0.47</td>
<td>6.6±0.28</td>
<td>0.60±0.06</td>
<td>3.24±0.11</td>
<td>92.15%</td>
</tr>
<tr>
<td>F6</td>
<td>Brownish Circular 10mm</td>
<td>250±0.71</td>
<td>6.7±0.31</td>
<td>0.52±0.03</td>
<td>3.18±0.03</td>
<td>95.63%</td>
</tr>
<tr>
<td>F7</td>
<td>Brownish Circular 10mm</td>
<td>250±0.47</td>
<td>6.3±0.31</td>
<td>0.65±0.09</td>
<td>3.20±0.22</td>
<td>91.33%</td>
</tr>
<tr>
<td>F8</td>
<td>Brownish Circular 10mm</td>
<td>250±0.48</td>
<td>6.7±0.28</td>
<td>0.61±0.02</td>
<td>3.18±0.03</td>
<td>87.39%</td>
</tr>
<tr>
<td>F9</td>
<td>Brownish Circular 10mm</td>
<td>250±0.47</td>
<td>6.8±0.28</td>
<td>0.65±0.09</td>
<td>3.20±0.22</td>
<td>80.58%</td>
</tr>
</tbody>
</table>
**In Vitro Drug Release Studies of SR tablets of Metoprolol Succinate**

The rate of drug dissolution from the tablet is frequently used to predict the rate of drug absorption for numerous drug moieties in the gastrointestinal tract. The effectiveness of the tablet product and variations in the bioavailability of the formulations may both be directly correlated with the rate of drug dissolving. Therefore, a tablet formulator's primary worry is frequently whether or not a tablet releases its drug content when placed in the milieu of the gastrointestinal tract. This dissolution test is frequently helpful for understanding the approximate drug release behaviour of dose forms in the GIT, including control release, sustain release, time dependent, targeted, etc.

**Table 15: Dissolution of sustained release metoprolol succinate matrix tablet of F6 batch.**

<table>
<thead>
<tr>
<th>TIME</th>
<th>%CUMULATIVE DRUG RELEASE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>22.223</td>
</tr>
<tr>
<td>4</td>
<td>33.273</td>
</tr>
<tr>
<td>8</td>
<td>58.741</td>
</tr>
<tr>
<td>20</td>
<td>95.633</td>
</tr>
</tbody>
</table>

![Dissolution profile](image)
Drug release kinetic studies of tablet formulation

Formulation F6 shows significant good release for 20 hrs with low burst effect. The formulation having concentration 20mg of aegle marmelos and 7.5mg PVPk30 exhibited the extended cumulative percentage of drug release value (95.633%) after 20 hr of gum. The drug release follows the Higuchi release pattern i.e. diffusion followed by erosion.

<table>
<thead>
<tr>
<th>Formulations</th>
<th>Zero order kinetics</th>
<th>First order kinetics</th>
<th>Higuchi square root equation</th>
<th>Regression coefficient (r)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F6</td>
<td>0.9231</td>
<td>0.9145</td>
<td>0.9990</td>
<td>0.5176</td>
</tr>
</tbody>
</table>

Table 16: Drug release kinetic studies of tablet formulation

STABILITY STUDY-

The chosen ideal formulation was subjected to stability tests over a period of three months at 45°C, 2°C, and a relative humidity of 75% to 5% at room temperature. Table 23 shows the dissolution profile following stability testing at the aforementioned temperatures and humidity conditions. The results showed that the tablets didn't change physically (in terms of hardness or friability) over the course of the study, and tests conducted at room temperature after three months revealed drug release levels above 90.23 and 92.45 percent. This demonstrates that pills are typically stable when kept.

Table 17: Physico-Chemical Evaluation Of Selected Matrix Tablets Before And After Stability Study

<table>
<thead>
<tr>
<th>ICH conditions</th>
<th>Hardness test (kg/cm2)</th>
<th>% Drug Release</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>45 ±2°C/75 ± 5% RH</td>
<td>6.7±0.31</td>
<td>6.9±0.31</td>
</tr>
<tr>
<td>Room Temp.</td>
<td>6.7±0.31</td>
<td>6.8±0.24</td>
</tr>
</tbody>
</table>
DISCUSSION—Modern medicine administration systems frequently employ the oral modified discharge dose formulations. Reducing medication dosage repetition and total dose with the SR lattice framework lowers the medication's side effects. One of the drugs that the network SR structure distributes throughout the G.I. parcel is metoprolol succinate, which reaches its maximal medicine release level quickly before progressively slowing down over time. Regular biopolymers should be used instead of synthetic polymers because of their extensive benefits. The initial clusters of details were completed and evaluated; out of five groups, group P5 demonstrated the release of medication in accordance with USP. This shows that using aegle Marmelos 20 mg is the optimal convergence. F6 is the optimal plan, according to future research employing a 32 factorial plan, to demonstrate the most intense pharmaceutical release. The results of the current review reveal that conventional gums were regarded as useful in identifying the assisted delivery lattice tablets of metoprolol. It became clear that the 20 mg gums' centralization was suitable for delaying the arrival of medication for 20 hours and successful in creating the sustained-release matrix tablets of metoprolol.

CONCLUSION—The conclusions reached after the tests were summarised as follows: For metoprolol succinate in purified water at max 223 nm, an appropriate logical technique was developed in light of a UV-Visible spectrophotometer. Prior planning prevented the introduction of hydrophilic drugs (Metoprolol Succinate) The Matrix, which supported the delivery of items like aegle marmelos in the past, is compatible with metoprolol succinate. Evaluation of aegle marmelos for assisted discharge grid tablet of metoprolol succinate was laid out. Metoprolol Succinate supported discharge lattice tablets were successfully pre-arranged using aegle marmelos and other excipients. Pharmacopoeial and non-pharmacopoeial (industry defined) testing were performed on the tablets. Metoprolol Succinate's oral supported discharge drug delivery system delivers the medication for up to 20 hours in a controlled manner, allowing for the achievement of the ideal restorative profile with the least amount of medication used, work on understanding consistency, and reduced drug opposition. The review revealed sophisticated details F6, which followed Higuchi square root dynamic models, and an instrument for drug discharge that was perceived as dispersion then disintegration. In this way, an effort to develop a potent detailed innovation was feasible, had little side effects, and focused on maintaining consistency.

Future Scope: In vivo reads up prompting IVIVC for commercialization Improve the public economy by giving cheap detailing to individuals utilizing locally accessible material.

REFERENCES


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Declarations-

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and material

The database used and analyzed during the current study are available from the corresponding author on reasonable request.

Competing intrest

The authors declare that they have no competing interests

Funding

Not applicable

Authors contribution

All authors have same contribution.

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