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A Review on Nitroglycerin as Potent Vasodilator

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A B S T R A C T

Coronary artery disease (CAD), a prevalent form of cardiovascular disease, results from the narrowing or blockage of coronary arteries due to plaque build up an inflammation. This review explores the pathophysiology of chronic CAD, emphasizing the role of inflammation in atherosclerosis and its cellular mechanisms. Nitroglycerin, cornerstone in the management of CAD, is analyzed for its pharmacological mechanisms therapeutic applications, and challenges like tolerance development. Detailed insights nitroglycerin's physicochemical properties, synthesis, and stability are provided, highlighting its dual role as a vasodilator and a therapeutic agent. This article aims to consolidate current knowledge and address gaps in the understanding and utilization of nitroglycerin in CAD management.

Keywords: Nitroglycerin (NTG), Pathophysiology, Nitric oxide (NO), Atherosclerosis.

1.INTRODUCTION

Cardiovascular diseases (CVDs) are a group of conditions that affect the heart and blood vessels. They are chronic illnesses that develop slowly over time and often show no symptoms for many years. Coronary artery disease (CAD) is one of the main causes of CVDs Coronary artery disease (CAD) is a common heart condition where the major blood vessels (coronary arteries) that supply the heart with blood become narrow or blocked. This usually happens because a fatty substance, called plaque, builds up inside the inner layer of the artery wall. Along with this plaque buildup, there's often inflammation, especially if it becomes long term. These changes make it harder for blood to flow to the heart muscle cells, which reduces their supply of oxygen and nutrients.(1)

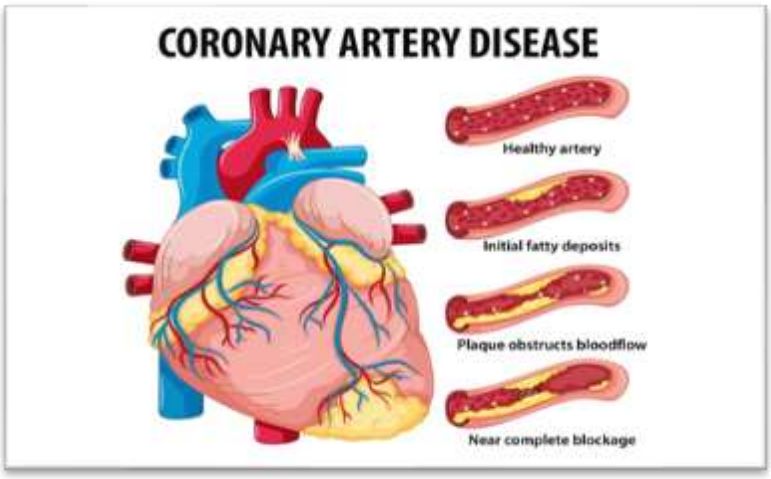

Fig.1 Coronary Artery Disease

1.1 Sign and symptoms of CAD:-

1. Chest pain (angina), fullness or pressure
2. Fatigue
3. Heart palpitations, or sensations of a racing heartbeat

4 Swelling in the hands or feet [(2)]

1.2 Causes of CAD :-

1. Overweight
2. Physical inactivity
3. Unhealthy eating [(3)]

1.3 The Pathophysiology of Chronic CAD:-

a complex process involving multiple risk factors and a lot of cellular communication. Atherosclerosis, once thought to be mainly a problem of cholesterol buildup, is now understood as Inflammation plays a big role in every step of atherosclerosis, contributing not only to plaque buildup but also to heart-related complications.

The process begins when the inner layer of artery walls (endothelium) encounters harmful substances, like certain bacteria, high cholesterol levels, or high blood pressure signals. These factors trigger the cells of the artery walls to produce molecules that attract white blood cells to stick to the artery's inner lining. These white blood cells, mainly immune cells like macrophages and T cells, migrate into the artery wall and communicate with other cells there, like smooth muscle cells (SMCs) and endothelial cells.

These interactions are controlled by various inflammatory molecules, including certain fats and proteins called cytokines. The SMCs begin to move from deeper layers of the artery wall to the inner layers, where they multiply and produce a complex mesh of fibers and proteins called the extracellular matrix.

In this environment, molecules called matrix metalloproteinases (MMPs) are also produced, which help shape and remodel the artery structure. These MMPs, in balance with other inhibitors, control cell activities like growth, movement, and death. The extracellular matrix also traps cholesterol carrying molecules, which become modified and contribute to inflammation. Over time, these modifications lead to a stronger immune response, which accelerates the buildup of plaque.

As plaques grow, they may start to harden (calcify) in a way similar to bone formation. Cell death within these plaques adds to the complexity, creating a mix of fats and immune signals that form a central “necrotic core.” This necrotic core can make the plaque more prone to rupture, increasing the risk of serious cardiovascular events.[(4)]

2. NITROGLYCERIN:-

Nitroglycerin (NTG) provides significant relief from angina pectoris for patients with coronary artery disease, but its mechanisms of action are complex and, in some ways, debated. NTG is believed to reduce the myocardial oxygen demand by decreasing systolic wall tension, which it achieves by lowering systemic pressure (afterload) and reducing left ventricular (LV) diastolic pressure and cavity size (preload). By lowering intraventricular diastolic pressure, NTG enhances the distribution of blood flow through the myocardium by reducing the external diastolic compression on the subendocardial vessels. Although NTG doesn’t significantly dilate the coronary arteriolar resistance bed, it does dilate coronary collaterals and healthy large coronary arteries.(5) Nitroglycerin was first formulated as a short-acting nitrate preparation for clinical use in 1879, and is the oldest and most commonly prescribed short acting anti-anginal agent.8,9Nitrates are now available in many delivery forms, from long-acting oral preparations, to cutaneous ointments, long acting transdermal patches, and intravenous formulations. This review will focus solely on short-acting, sublingual nitrates, which are the most underappreciated and possibly underutilized nitrates.Despite being in clinical use since 1879, there remains an important need to educate both patients and health care providers on the various benefits of short acting nitrates, particularly sublingual nitroglycerin, administered as sublingual tablets or spray10 in patients with angina. In the majority of patients with stable ischemic heart disease (SIHD), long-acting nitrates are used as part of OMT to reduce the risk of cardiovascular morbidity (notably angina and myocardial ischemia) and thus, to enhance the quality of life by reducing symptoms and improving exercise capacity.11– 13Under-appreciated is the fact that nitrates play an important role in the prophylactic treatment of angina caused by short-term physical or emotional stress. Similarly, prophylactic nitroglycerin should be used as part of an overall structured cardiac rehabilitation program for secondary prevention in patients with SIHD.(6)

2.1 Structure of Nitroglycerin:

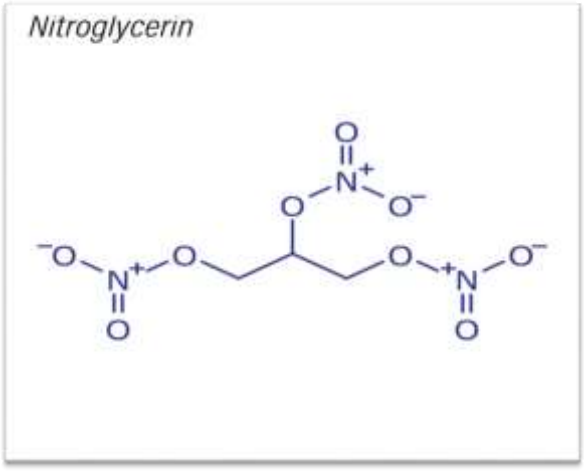

Fig 2 Structure of Nitroglycerin

- **IUPAC Name:-**1,2,3-Trinitroxypropane
- **Molecular weight:-** 227.0865 g/mol
- **Brand Name:-** Nitrostat
- **Melting point:-** 13.2°C
- **Boiling point:-** 218°C
- **Category:-** nitrates
- **Storage:-** Store the sublingual powder at room temperature, away from heat, moisture, and direct light.
- **Solubility:-** poorly soluble in water, with a solubility of about 1 mg/ml

3.MECHANISM OF ACTION :-

3.1 Effect on endothelial function:-

The endothelium is the inner lining of blood vessels, making it responsive to chemicals that either tighten or relax blood vessels. A healthy endothelium can produce substances that maintain normal blood vessel function. When the endothelium is damaged, it produces less nitric oxide (NO), a key molecule that helps relax blood vessels. Organic nitrates, like nitroglycerin, are converted into NO in the body and can help restore NO levels in patients with coronary artery disease (CAD). Increasing NO improves blood vessel function, which can lower the risk of heart disease by relaxing vessels, reducing platelet clumping, and preventing clot formation NO produced naturally in the body works locally, while therapeutic nitrates given as medication act more widely in the body. In atherosclerosis (plaque buildup in arteries), the endothelium remains mostly intact but produces less NO, which weakens its ability to relax blood vessels. Although the sensitivity to nitroglycerin may decline in advanced artery blockages, its effects generally remain strong. However, repeated use of nitrates like nitroglycerin can lead to tolerance (less effect over time), unlike naturally produced NO, which doesn't lead to tolerance. [6]

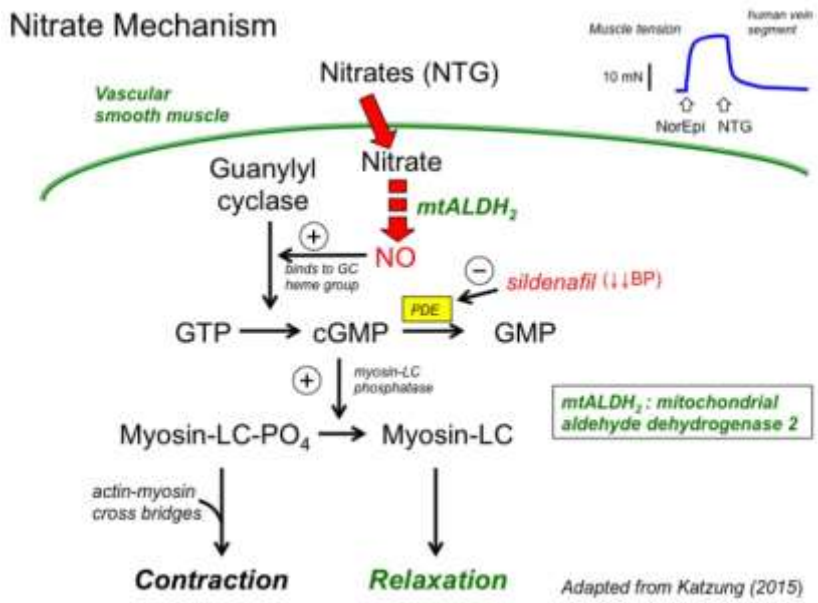

Fig 3 Mechanism of action of nitrates

3.2 Effect on flow-mediated dilation:-

Nitroglycerin has significant effects on both pulmonary artery diastolic pressure (PAPd) and peripheral arterial circulation, as shown by finger pulse wave analysis. When nitroglycerin is administered, PAPd decreases while the a/b ratio of the finger pulse wave increases, and these changes happen in a closely related, mirror-image pattern. This makes it possible to predict the effects on PAPd using finger plethysmography. A study by Tadamura et al examined the effects of nitroglycerin spray on myocardial blood flow (MBF) and coronary vascular resistance (CVR) in patients with coronary artery disease (CAD) and healthy individuals. The spray did not change overall MBF but specifically reduced CVR in areas of the heart muscle affected by ischemia (reduced blood flow). In these ischemic regions, the uptake of tracers (used to measure blood flow) increased compared to non-viable or healthy tissue.In general, nitrates like nitroglycerin act as vasodilators that do not rely on the endothelium (the inner lining of blood vessels) and are particularly effective in diseased coronary arteries with reduced nitric oxide (NO) production. They help relieve angina (chest pain) by improving blood flow to areas of the heart with reduced oxygen supply, increasing coronary collateral circulation, and improving aortic function. Nitrates also reduce the workload on the heart (preload) in patients with heart failure.[6]

3.3 Effect on platelets:-

Organic nitrates are processed in the body to produce nitric oxide (NO) or a similar compound, which strongly activates an enzyme in platelets called guanylate cyclase. This activation increases the levels of a molecule called cGMP in platelets, reducing the ability of fibrinogen to bind to the glycoprotein IIb/IIIa receptor. A study by Diodati and colleagues examined the effects of nitroglycerin (a type of organic nitrate) on platelet activity in patients with unstable angina or a heart attack. They found that a 45-minute nitroglycerin infusion reduced platelet aggregation by more than 50%. However, platelet activity returned to normal within15 minutes after stopping the infusion. Since platelet aggregation contributes to acute coronary syndromes, this platelet-inhibiting effect of nitrates may help improve blood flow to the heart's oxygen-deprived areas.[6]

4. SYNTHESIS OF NITROGLYCERIN :

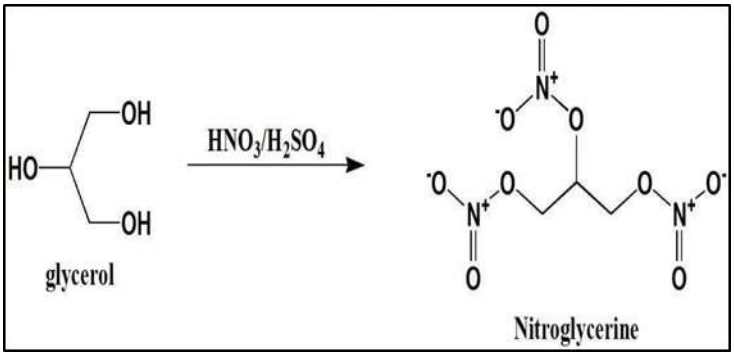

Fig 4 synthesis of Nitroglycerin

The image shows the synthesis of nitroglycerin from glycerol through a nitration reaction. Here's a summary of the process:

4.1 Steps of Nitroglycerin Synthesis:-

a. **Starting Material** – Glycerol: The process starts with glycerol, a molecule with three hydroxyl (-OH) groups.

b. **Nitration Reaction:** Glycerol reacts with a mixture of concentrated nitric acid (HNO_3) and sulfuric acid (H_2SO_4).

c. **Nitration of Glycerol:** The nitronium ions react with the hydroxyl groups of glycerol, replacing them with nitro groups ($-NO_2$) forming nitroglycerine

d. **Product – Nitroglycerin**: The final product, nitroglycerin, contains three nitro groups attached to the glycerol backbone, making it highly energetic and sensitive, thus commonly used in explosives [7]

5.ANALOGUE OF NITROGLYCERIN :-

Nitroglycerin is a highly effective vasodilator and an explosive compound. Its analogues can be classified based on their primary use in medicine and explosives:

5.1 Medical Analogues:-

Medical analogues of nitroglycerin are also nitrate esters used for similar cardiovascular purposes, such as treating angina or heart failure.

These include :

- **Isosorbide dinitrate:**

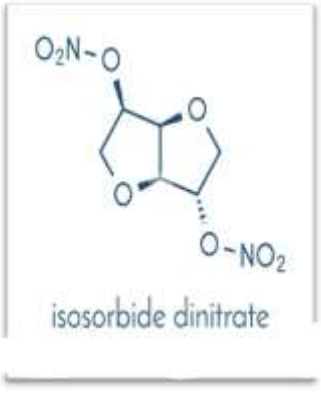

Fig [illegible] bide dinitrate

a. Used f[illegible]

b. Longer duration of action compared to nitroglycerin.

- **Isosorbide mononitrate:**

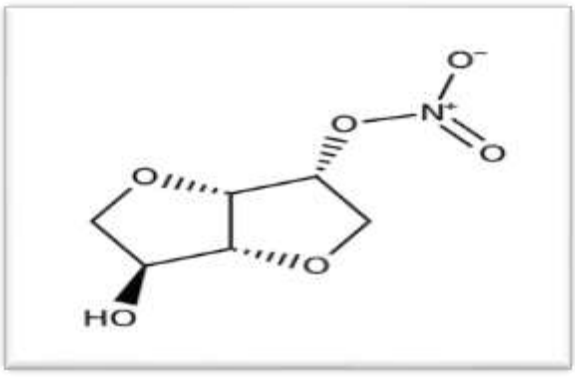

Fig 6 Isosorbide mononitrate:

a. A metabolite of isosorbide dinitrate.

b. Commonly prescribed due to better oral bioavailability.

- **Amyl nitrite:**

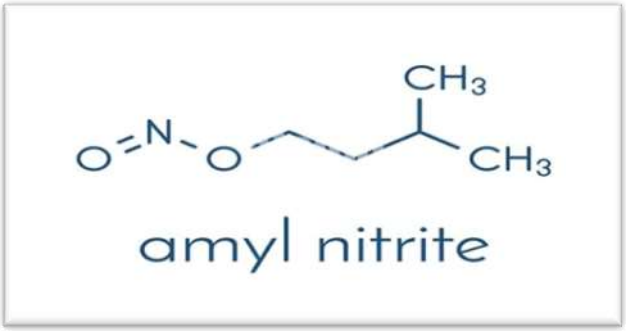

Fig 7 Amyl nitrite

i. A volatile liquid used as an inhalant for acute angina.

ii. Provides rapid relief by dilating blood vessels.[8]

6. EVALUATION PARAMETERS OF NITROGLYCERIN :-

6.1 Solubility:-

- **Nitroglycerin Solubility in Organic Solvents:-**

Nitroglycerin is a nitrate ester and is highly soluble in many organic solvents.

1. Ethanol: Nitroglycerin is highly soluble in ethanol due to its polar nature and the ability of ethanol to act as a hydrogen bond donor and acceptor, enhancing solubility.

2. Methanol: Similarly, nitroglycerin is soluble in methanol. Methanol's smaller molecular size may slightly enhance its solubility compared to ethanol.

3. Chloroform: Nitroglycerin is soluble in chloroform, a nonpolar solvent, due to favorable van der Waals interactions and the presence of nitroglycerin's nonpolar groups.

- **Buffer solubility:-**

The solubility of nitroglycerin (NG) in buffer solutions can vary depending on the pH, ionic strength, and the composition of the buffer. Here's a general overview of how different conditions can affect the solubility of nitroglycerin

1 Neutral to Slightly Alkaline pH (pH 7 - 8):-

Buffer Type: Phosphate buffer, Tris buffer, or bicarbonate buffer.

Effect: Nitroglycerin is poorly soluble in water at physiological pH (~7.4) due to its lipophilic nature. However, it is slightly more soluble in slightly alkaline conditions (pH 8), where its solubility increases marginally. Nitroglycerin is primarily in its neutral, non-ionized form in this pH range, which limits its water solubility.

Solubility: Around 1–2 mg/mL in water, potentially slightly higher in alkaline buffers.

2. Alkaline pH (pH 9 - 10) :-

Buffer Type: Sodium carbonate buffer, borate buffer.

Effect: At more alkaline pH levels, nitroglycerin becomes more ionized, which increases its solubility in aqueous solutions. The presence of an alkaline buffer can reduce the tendency of nitroglycerin to form aggregates, thus enhancing solubility in solution.

Solubility: Solubility can increase due to higher ionization of the compound, but nitroglycerin may degrade at these higher pH levels

3. Acidic pH (pH 3 - 6):-

Buffer Type: Acetate buffer, citrate buffer.

Effect: At acidic pH, nitroglycerin tends to remain in its neutral, non-ionized form. However, the solubility in acidic environments does not increase significantly compared to near-neutral or alkaline pH. Its solubility in such buffers is typically low, similar to water solubility.

Solubility: Around 1–2 mg/mL or slightly lower in acidic buffer solutions. This pH range does not significantly enhance its solubility compared to neutral conditions. [9]

6.2 Stability:-

Nitroglycerin (NG), or glycerol trinitrate, is a highly sensitive and volatile compound that can undergo decomposition under various conditions. Its stability is influenced by temperature, light, humidity, and the presence of impurities or catalysts. Here's an overview of how different conditions affect its stability:

1.Temperature:-

a. Nitroglycerin is sensitive to heat. At high temperatures, it becomes increasingly unstable and can decompose rapidly, potentially leading to detonation.

b. At low temperatures, NG is generally stable, but it can become more viscous and difficult to handle.

c. Storing it at temperatures below 25°C (room temperature) is recommended for its stability.

2 Light:-

a. Exposure to light, especially ultraviolet (UV) light, can promote the decomposition of nitroglycerin, causing it to lose potency and possibly degrade into harmful products.

b. For this reason, NG is typically stored in dark-colored containers to minimize light exposure.

3. Humidity:-

Nitroglycerin is sensitive to moisture. High humidity can promote the degradation of NG, especially when stored improperly. The compound is generally stable in low humidity environments, which helps in maintaining its chemical integrity.

4. Presence of Impurities:-

a. Contamination with impurities, such as metal ions (copper, iron), can catalyze the decomposition of nitroglycerin, causing it to break down more rapidly.

b. Nitroglycerin should be kept away from reactive substances to minimize the risk of decomposition.

5. Pressure:-

Under normal atmospheric pressure, nitroglycerin is relatively stable, but at higher pressures (such as in confined spaces), the risk of accidental detonation increases.

6 . Concentration:-

Higher concentrations of nitroglycerin (as found in some industrial applications) are more unstable and pose a greater risk of detonation compared to dilute solutions used in pharmaceuticals (such as in nitroglycerin tablets or sprays for heart conditions.[10]

6.3. Melting point:-

Melting Point of Nitroglycerin:

The melting point of nitroglycerin (NG) is:

13.4 - 14.2°C (56.1 - 57.6°F)

The melting point of nitroglycerin is 18°C (64.4°F). This relatively low melting point means that nitroglycerin is a liquid at room temperature and can freeze into a solid at temperatures below 18°C. [11]

6.4 Boiling point :-

Boiling Point of Nitroglycerin:

The boiling point of nitroglycerin (NG) is:

- 160-170°C (320-338°F) at 760 mmHg (standard pressure) - 80-90°C (176-194°F) at 10 mmHg (reduced pressure)

Importance of the Boiling Point of Nitroglycerin:

1. **Stability at High Temperatures:**

The high boiling point of nitroglycerin ensures that it remains stable as a liquid at room temperature and under typical conditions. However, if heated beyond its boiling point, nitroglycerin may begin to decompose and could detonate due to its instability when exposed to heat. This highlights the importance of controlling temperature when working with or storing nitroglycerin.

2. Safety in Storage and Transport:

Knowing the boiling point of nitroglycerin is crucial for safely transporting and storing it. If nitroglycerin were to be heated near its boiling point, it could pose a significant safety hazard, as its decomposition could lead to an explosion. It is necessary to avoid environments or containers that might allow nitroglycerin to reach this temperature.

Nitroglycerin is sensitive to not just shock and friction, but also high heat. Its boiling point provides a threshold beyond which it is at a high risk of undergoing dangerous decomposition, releasing gases and causing an explosion. This is why temperature control, including avoiding overheating, is vital when handling or using nitroglycerin.

3 . Use in Explosives:

In its practical use as an explosive (e.g., dynamite), nitroglycerin is mixed with other materials to stabilize it. Understanding its boiling point helps in designing safe explosives, ensuring that the substance can be stored and handled without risk of spontaneous detonation due to heat. This characteristic also helps determine the ideal conditions for detonating the compound under controlled circumstances [(12)]

6.5 Pka:-

PKa of Nitroglycerin:-

The pKa values of Nitroglycerin (NG) are:

pKa1 = 6.6 (nitro group 1)

pKa2 = 8.5 (nitro group 2)

pKa3 = 10.3 (nitro group 3)

1. Experimental Methods:-

UV-Vis Spectroscopy: In some cases, the absorption spectrum of nitroglycerin might be used to study its ionization, although this method is not common for such unstable compounds.

2. Theoretical Calculations:

Computational Chemistry: Quantum mechanical methods, such as density functional theory (DFT), can be used to model nitroglycerin and predict the pKa based on molecular structure and ionization energies[(13)]

7 BRAND PRODUCT OF NITROGLYCERIN :-

7.1. GTN Sorbitrate -CR 6.4 mg Tablet:-

- Medicine name:- GTN Sorbitrate -CR 6.4
- Manufactured by :- Sun pharma
- API:- Nitroglycerin
- Strength:- 6.4mg
- Brand name :- GTN- Sorbitrate-CR [(14)]

Fig 8 GTN Sorbitrate -CR 6.4

7.2. Nitrolong 2.6 Tablet CR:-

- Medicine name:- Nitrolong 2.6
- Brand Name:Nitrolong
- Strength: 2.6 mg
- API:-Nitroglycerin (GTN)
- Manufactured by :- Mankind Pharma Ltd .[15]

Fig 9 . Nitrolong 2.6

7.3 Myonit SR 2.6 Tablet:-

- Medicine name :-Myonit SR
- Manufacturer: Cipla Ltd.
- Strength: 2.6 mg
- API:- Nitroglycerine [16]

Fig 10 Myonit SR 2.6

7.4. Angispan 6.5 mg capsule:-

- Medicine name :-Angispan - TR
- Manufacturer: Torrent pharmaceuticals Ltd.
- Strength: 6.5.mg
- API:- Nitroglycerine [17]

Fig 11 Angispan 6.5 mg

7.5 Nitroglycerin Injection 5 mg :-

- Medicine name :Nitroglycerin Injection
- Manufacturer: Cipla Ltd.
- Strength: 5 mg
- API:- Nitroglycerin([16]

Fig 12 Nitroglycerin Injection

8. CONCLUSION :-

CAD remains a leading cause of morbidity and mortality worldwide, but it is largely preventable and manageable through early diagnosis, lifestyle modifications, and appropriate medical or surgical interventions. Strategies such as maintaining a healthy diet, regular physical activity, smoking cessation, stress management, and controlling risk factors like high blood pressure, diabetes, and cholesterol levels are critical for prevention and treatment. Advances in medical therapies and procedures, such as angioplasty and coronary artery bypass grafting, have significantly improved outcomes for individuals with CAD. Regular follow-up and adherence to treatment plans are essential for long-term health and quality of life. This review underscores the importance of integrating pharmacological strategies with lifestyle modifications for comprehensive CAD management. Further research is necessary to refine nitroglycerin formulations, overcome tolerance issues, and enhance therapeutic efficacy in patients with stable ischemic heart disease.

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