# FORMULATION AND COMPATIBILITY OF ADMIXTURE STUDY FOR SODIUM NITROPRUSSIDE INFUSION

***Dissertation work submitted to***
***The Tamil Nadu Dr.M.G.R Medical University Chennai***
***In partial fulfilment of the degree of***

**MASTER OF PHARMACY**
**IN**
**PHARMACEUTICS**


Submitted by
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**NOVEMBER 2019**


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## DECLARATION

I hereby declare that this dissertation entitled **"FORMULATION AND COMPATIBILITY OF ADMIXTURE STUDY FOR SODIUM NITROPRUSSIDE INFUSION "**submitted by me, in partial fulfillment of the requirements for the degree of **MASTER OF PHARMACY IN PHARMACEUTICS** to The Tamil Nadu Dr.M.G.R Medical university, Chennai is the result of my original and independent research work carried out under the guidance **Dr.T.AKELESH**, M. Pharm., Ph.D.,AssociateProfessor, Department of Pharmaceutics, RVS College of Pharmaceutical Science.

Place: Coimbatore **DAVID S**

Date:

# CERTIFICATE

This is a bonafide dissertation on **"FORMULATION AND COMPATIBILITY OF ADMIXTURE STUDY FOR SODIUM NITROPRUSSIDE INFUSION"** by **DAVID S** the work mentioned in the dissertation was carried out in the Department of Pharmaceutics at R.V.S College of Pharmaceutical Sciences, Sulur , Coimbatore and this work is supervised by me in the academic year 2018-2019.

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# EVALUATION CERTIFICATE

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# INTRODUCTION[17]

- Intravenous (IV) administration of many sterile drug products requires admixture preparation using a diluent prior to administration.
- A pharmaceutical admixture consists of a drug product mixed with an appropriate diluent in a suitable dosing/ delivery device for the purpose of parenteral infusion to the patient.
- Regulatory agencies, as a part of registration requirements, have listed specific requirements for the demonstration of the compatibility of the drug product with the diluents and with the infusion devices.
- For example, as per **ICH Q8** guideline,
- The compatibility of the drug product with reconstitution diluents should cover the recommended in- use shelf life, at the recommended storage temperature and at the likely extremes of concentration (ICH 2009 ). Similarly, guidance for industry from the U.S.
- Food and Drug Administration states that for parenteral dosage forms, the appropriate containers, filters, and tubing materials should be identified (US Department of Health and Human Services and Drug Administration 2010 ).
- Therefore, admixture compatibility and stability studies, which may include evaluation of the compatibility and in-use stability of the drug product with the diluents as well as the dosing/delivery devices, are key components of the pharmaceutical development process.
- The importance of admixture compatibility and stability studies is further magnified by the fact that in most cases the patient is exposed to the admixture and not the undiluted drug product.
- In spite of the high relevance, there is limited literature available for scientists and the drug development community to provide guidance on the design and execution of these admixture compatibility and stability studies. Although each product may have specific requirements,
- The general aspects of admixture compatibility and stability studies remain unchanged and may be applicable to all sterile products intended for IV administration.

- The purpose of this chapter is to discuss various challenges associated with conducting admixture compatibility and stability studies and the related regulatory guidance.

## Background:

### Diluents:

The most commonly used diluents for IV administration are:

- 0.9 % sodium chloride injection, USP (normal saline),
- 5 % dextrose injection, USP (D5W),
- Ringer's Injection, USP and Lactated Ringer's Injection, USP.

In most cases, the diluent solution is iso-osmotic.

Therefore, the drug upon significant dilution with the diluent is expected to be Iso-osmotic.

In some cases the diluent may be supplied as concentrated solution and is expected to be diluted with appropriate amounts of drug to obtain iso-osmotic solution for IV administration.

As an example, 10 % Dextrose Injection, USP, hypertonic solution, is supplied with the expectation that it will be diluted with a compatible IVfluid to provide a 5 % final dextrose concentration for intravenous infusion.

## Components:

During clinical administration, the drug admixture may come into contact with the following components:

- **IV container**—In many instances, the drug admixture may be prepared up to 24 h prior to dosing in the IV container.
- **Infusion line**—The admixture comes in contact with the infusion line during infusion, which may last between a few minutes to a few hours.
- **IV catheter**—The catheter usually has a much smaller contact area. However, a peripherally inserted catheter line which is considerably longer may have significant contact with the drug admixture.

- **Filters**—Filters of 5 μm or smaller pore size (either in-line or add on) are commonly used during infusion to remove any adventitious particles from the admixture.
- **Syringes**—In cases where the infusion volume may be small the dose may be administered through a syringe pump (e.g., pediatric patients).

Another component that may need to be evaluated is the infusion pump.The use of peristaltic infusion pump instead of gravity assisted drip does not involve contact with the drug. However, the use of pump in the case of biologics may potentially cause drug degradation due to high sheer-related stresses .

**Materials of Construction:**

- Historically, IV containers and infusion lines were made from polyvinyl chloride (PVC).
- The main reasons for using PVC-based materials are their high strength and flexibility, transparency, ease of sealing, good resistance to sterilization procedures, and relatively low cost .
- PVC-based infusion devices are made flexible by addition of bis(2- ethyl hexyl) phthalate (DEHP) as a plasticizer.
- However, since the DEHP is not chemically bonded to PVC, it can leach into the drug solutions, especially those containing non aqueous components such as fats or surfactants.
- There have been increasing concerns of adverse health effects of DEHP (US Food and Drug Administration 2010 ).
- An alternative to DEHP plasticized PVC is Tri-2-ethylhexyl tri mellitate (TOTM) plasticized PVC, which is believed to have lower toxicity (ExxonMobil Biomedical and has been shown to have lower migration rates.
- Another alternative is to use a PVC container that is lined with polyethylene (PE) on the fluid contact surface.
  PE is believed to act as a barrier and minimize the migration of plasticizer DEHP into the drug solution.
- Moreover, other non-PVC materials have also emerged as alternatives, e.g., ethyl vinyl acetate (EVA) and poly olefins Table 17.1 lists the representative materials of construction of IV containers and infusion lines that are currently available.

Representative materials of construction a of IV containers and infusion lines IV containers Infusion lines

- ✓ PVC + DEHP
- ✓ PVC + TOTM
- ✓ EVA
- ✓ Poly olefin (non-PVC, non-EVA)
- ✓ Poly olefin/polyamide co-extruded plastic with PE lined fluid contact surface
- ✓ PVC + DEHP
- ✓ PVC + TOTM
- ✓ PE lined PVC
- ✓ Polyolefin a In order to determine the material composition,

**Challenges of Admixture Studies**:

How to Design an Efficient Study to meet all Requirements of Clinical Dosing?

- ➢ It is critical to define the scope of the admixture study based on the clinical dosing strategy.
- ➢ In most cases the information about clinical dosing plan is limited to the dose range defined in terms of mg of dose per kg of patient weight (mg/kg, mpk) or mg of dose per unit patient body surface area (mg/m 2 ).
- ➢ The scope of the admixture study may include the definition of admixture concentration levels to be tested, identification of suitable IV container/infusion line type, and identification of the size of IV container and fill volumes from the perspective of worst case scenarios.
- ➢ The goal is to provide maximum flexibility to the clinicians while minimizing the number of experiments and required study materials.

**Admixture Concentration Levels**:

- ➢ The goal of the admixture compatibility and stability studies should be to evaluate suitable concentration range that would allow administration of all the desired dose levels in the clinic for a range of patient weights.
- ➢ Therefore, testing the lowest and highest concentrations required in the clinic can bracket the entire concentration range.

- The first estimation of the lowest and the highest concentration levels can be made considering the lowest dose level/lowest patient weight and highest dose level/highest patient weight combinations for representative IV container sizes.
- However, in some cases there could be analytical challenges associated with the low concentration limit, which would require increasing the concentration.

**Analytical Challenges**:

***Concentration level below levels of quantification.***

As discussed in the admixture studies could be bracketed by using two concentration levels calculated from the lowest and the highest dose to be given in the clinic.

While the upper concentration limit may be in the same order of magnitude as the concentration of the undiluted drug product and therefore usually not challenging from an analytical perspective, the lower concentration limit could occasionally be much lower than the analytical level of quantifcation.

As an example for biological products such as monoclonal antibodies, the lower concentration limit of 0.05 mg/mL in may be challenging from analytical perspective.

In such scenarios, suitable adjustments need to be made either to the dosing plan or analysis. For low dose levels, the total admixture volume in the IV container may need to be lowered to ensure analytically feasible concentration. Sample replicates.

It is best to have samples tested in triplicates for optimization of precision of measurement. In practice, though, this may lead to a significant increase in the number of samples and drug product requirements.

Therefore, duplicate samples may be a viable option. In the cases where the duplicate sample loads are still too high, average sample composites may be considered.

In such a situation, the actual analytical sample will be a composite of two or more individual samples prepared in the same way.

Even though a single sample will be tested, it will reflect an averaging of the conditions of individual samples. Admixture sample storage prior to testing.

In certain cases where the samples cannot be tested immediately, or if the samples are required to be shipped to different testing sites, they may be frozen to minimize changes.

However, a probe study or prior experience should be used to evaluate the effect of freezing on sample stability. Limited sample volume .

Composite samples may also be used if sample volume is limited. As an example, particulate matter testing by USP light obscuration requires approximately 25–30 mL of sample. However, an infusion line may only contain a total line volume 10 mL.

In this case, multiple infusion lines will need to be combined to generate sufficient volume for the Light Obscuration characterization Impurities in the diluent. Certain diluents may contain impurities which can interfere with the analytical techniques employed to test admixture samples.

For example, 5-hydroxymethylfurfural or related substances in Dextrose Injection, USP solution are degradation products of dextrose and absorb UV light (~280 nm), thus interfering with the UV A280 concentration measurements (USP 2004 ). Need to test diluent .

Certain tests may require measuring the diluent samples for assessing any background signal. In most cases it may be sufficient to collect diluent sample at the initial time point since no changes are expected during the course of the admixture study.

For example, particulate matter testing by HIAC may need background particle count of the diluent solution. Diluent measurement may also be required if it contains an impurity interfering with UV assay measurement. In certain cases the diluent may need to be run through assay to identify any interactions with the drug over time. Based on individual study needs, appropriate diluent sampling scheme should be used.

**IV Container Over fill Volume:**

IV containers filled with diluents usually contain an overfill volume to ensure that the label claim volume is met.

A published study with 162 D5W IV containers from different vendors found that the mean volume was 110.20 mL for 100 mL containers.

We have also found that 250 mL normal saline IV containers from one vendor had over fill volumes ranging from approximately 12 to 30 mL.

If the excess fill volume is not considered, the concentration of the study drug in the admixture solution can be off target and may lead to undesirable consequences related to under-medication.

Therefore, the concentration range covered in the admixture study may be made slightly broader than that required in the clinic to accommodate for concentration variations due to container overfill.

To precisely achieve target concentrations during admixture studies, the dilutions can be prepared by weight.

However, assuming that the pharmacist in the clinic would require a simpler process, it is recommended to test a statistically significant number of IV containers (e.g., 10 containers) to determine the average overfill volume and provide this information to the clinic.

It is important to note here that even though failure to consider overfill will results in an off-target concentrations (over dilution), the patient would still receive the total intended amount of drug as long as the entire container is dosed followed by infusion line flush, assuming there are no incompatibilities associated with over dilution.

Over fill volume would not be an issue if an empty IV container is being used to prepare the admixture since the required amount of diluent can be accurately added to the container.

However, this approach introduces additional manipulation steps of removing the diluent from another source and adding it to the empty container.

**Leachables :**

Generally, many of the stability indicating assays for the admixture solution are product-related.

For example, acceptance criteria for stability include monomer concentration (for biologics), product purity, and sub visible particulate matter levels in solution.

However, the presence of leachables from the infusion device contact material is often overlooked. Excipients, which are used to stabilize the drug product formulation, may also facilitate leaching within the admixture solution.

For example, excipients used to solubilize insoluble compounds in the drug product may also solubilize less soluble compounds from contact material that ordinarily would not leach.

For biologic products, surfactants such as polysorbate 80 (PS80) and polysorbate 20 (PS20) are commonly used to minimize the interaction of the drug with various interfaces encountered during manufacturing, storage,

**Acceptance Criteria:**

The analytical tests employed in the study should be able to detect any physical and chemical degradation of the drug molecule during storage in the admixture solution.

The typical tests that can be conducted for therapeutic proteins may include assay by UV A280, purity by HP-SEC, charge profile by HP-IEX, biological potency, pH, physical appearance, osmolality, and sub visible particulate matter count.

Small molecules may require assay and degradation products by HPLC, pH, physical appearance, osmolality, and sub visible particulate matter count.

In most cases, the analytical tests being used in the admixture study will be the same as those used for testing and release of the drug product.

Therefore, drug product release specifications can be used as a guide while setting acceptance criteria for the analytical tests of admixture study.

**Regulatory Requirements**:

Regulatory agencies, as a part of registration requirements, have listed specific requirements for the demonstration of the compatibility of the drug product with reconstitution diluents and with the infusion containers.

As an example the "ICH Harmonized Tripartite Guideline—Pharmaceutical Development Q8" states the following: "The compatibility of the drug product with reconstitution diluents (e.g., precipitation, stability) should be addressed to provide appropriate and supportive information for the labeling.

This information should cover the recommended in- use shelf life, at the recommended storage temperature and at the likely extremes of concentration.Similarly, admixture or dilution of products prior to administration

***(e.g., product added to large volume infusion containers) might need to be addressed" (ICH 2009).***

In addition, there are specific requirements listed in the Dosage and Administration section of labeling required by **21 CFR 201.57**(c)(3) as described in the Guidance for Industry document titled

***"Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products—Content and Format" (US Department of Health and Human Services and Drug Administration 2010).***

These include:

- Procedure to reconstitute the drug product (if applicable)
- Dilution procedure to form admixture solution
- Specific handling instructions (shaking, shear) to maintain stability of the biological drug product.
- Allowable concentrations of the admixtures.
- Storage conditions and durations.
- Compatible IV container and infusion line materials and allowable IV container sizes.
- Compatible diluents.
- Specific dosing instructions Based on the discussions provided in the previous section,it is clear that appropriate design of admixture studies plays a critical role in fulfilling these regulatory requirements.

# LITERATURE REVIEW

**Karnatz NN et al.,**The stability of esmolol hydrochloride and sodium nitroprusside in an admixture containing both drugs was studied. Solutions containing sodium nitroprusside in a final concentration of approximately 200 micrograms/mL and esmolol hydrochloride in a final concentration of 10 mg/mL in 5% dextrose injection were prepared in a 250-mL volumetric flask. The flask was wrapped with a light-protective cover, stored at ambient room temperature (15-30 degrees C), and protected from light. All experiments were conducted in triplicate with samples taken at 0, 2, 4, 8, and 24 hours. Testing included measurement of pH and absorbance at 400 and 600 nm. High-performance liquid chromatography was used to measure esmolol hydrochloride and sodium nitroprusside concentrations. No changes were observed in the physical appearance, pH, or absorbance of the admixtures. Neither the esmolol hydrochloride nor the sodium nitroprusside concentrations varied by more than 4% during the study. Under the conditions studied, esmolol hydrochloride is compatible with sodium nitroprusside in an admixture containing both drugs.[1]

**Horrow JC et al.,** Nitroprusside, however, is considered incompatible with all other medications. Critically ill patients who require multiple infusions of vasoactive and inotropic medications would benefit if physicians had additional information regarding compatibility of nitroprusside with other commonly used infusions. Utilizing high-performance liquid chromatography, the authors investigated the physical and chemical compatibility of nitroprusside, dobutamine, and nitroglycerin in solutions of 5% dextrose or 0.9% NaCl at clinically relevant concentrations. All drugs were present within the guidelines of the U.S. Pharmacopeia (+/- 10%) over 24 h in NaCl, but nitroglycerin degraded over 24 h when the three drugs were mixed in dextrose. We recommend diluting these medicines in NaCl when mixtures of them would exist for greater than 4 h.[2]

**Schulz LT et al.,**Admixtures containing both agents may provide a safe and effective alternative to more expensive agents used to reduce blood pressure in the critically ill patient. This study determined the physical and chemical stability of a 1:10 nitroprusside:thiosulfate admixture, stored up to 48 hours. The economic consequences of a shift toward using thiosulfate and nitroprusside, and away from higher cost alternatives, are considered.The combination of nitroprusside and thiosulfate is chemically and physically stable as a single compounded dose for up to 48 hours when stored at room temperature and

protected from light. The admixture represents an inexpensive option to other higher cost alternatives such as nicardipine or clevidipine.[3]

**Grillo JA et al.,** Determine the chemical compatibility of three different triple drug admixtures diluted with either 5% dextrose in water or 0.9% NaCl solution when administered via a multiple line infusion system (Omni-Flow 4000, Abbott Laboratories, Abbott Park, IL). The triple drug admixtures were: a) dobutamine, dopamine, and norepinephrine; b) nitroglycerin, sodium nitroprusside, and dobutamine; and c) nitroglycerin, dopamine, and dobutamine.

Two phase in vitro compatibility study.Phase I assessed chemical stability when the triple drug admixture was placed in a single container. In phase II, individual drug components of the admixtures were infused via the multiple line infusion system. Samples were collected at time 0, 1 hr, 2 hrs, 4 hrs, 12 hrs, and 24 hrs. All samples were frozen and stored at -70 degrees C until assayed.Samples were assayed using stability-indicating high performance liquid chromatography. The triple drug admixtures were considered to be chemically stable if there was < or = 10% loss of stated potency over 24 hrs. In phase I, chemical stability was observed for all triple drug admixtures at 24 hrs. In phase II, dobutamine, dopamine, norepinephrine, and sodium nitroprusside showed chemical stability at 24 hrs. Nitroglycerin showed a two-fold increase in concentration at 24 hrs compared with the initial concentration through the test infusion system; however, this amount was still one third lower than originally anticipated.All triple drug admixtures were chemically stable when placed in single containers. Dobutamine, norepinephrine, and sodium nitroprusside showed chemical stability when delivered via a multiple line infusion system.[4]

**Pramar Y et al.,**The solutions of dobutamine hydrochloride (5 mg/ml), dopamine hydrochloride (4 mg/ml), nitroglycerin (1 mg/ml) and sodium nitroprusside (1 mg/ml) in dextrose 5% injection were stable for 24 h when stored at 25 degrees C in 60-ml plastic syringes. For sodium nitroprusside, the syringes must be wrapped with aluminium foil (provided by the manufacturer), otherwise the loss in potency is very high (22%). There was no change in the pH values of dobutamine and dopamine solutions as well as sodium nitroprusside solutions in the prewrapped syringes. However, the pH value of nitroglycerin solutions decreased to 4.3 from 4.6 and that of sodium nitroprusside solutions in unwrapped syringes from 4.2 to 3.5; these solutions had discoloured. The chromatogram also showed

new peaks from the products of decomposition. The physical appearances of the other solutions did not change.[5]

**Agrawal A et al.,** stated that Sodium nitroprusside was recently suggested as a treatment option for cerebral ischaemia in patients with severe medically refractive vasospasm after subarachnoid haemorrhage.Intraventricular sodium nitroprusside represents a promising method of treatment for established delayed cerebral vasospasm and cerebral ischaemia refractory to conventional treatment.[6]

**Su Q et al.,** stated that to evaluate the clinical efficacy and safety of nitroprusside injection for preventing the slow-flow/no-reflow phenomenon after percutaneous coronary intervention (PCI). We searched the Cochrane Central Register of Controlled Trials (Issue 2, 2011), PubMed, EMbase, and Google Scholar for data. Two reviewers independently evaluated the quality of the included studies and extracted the data. A meta-analysis was performed using RevMan 5.0 software. Four randomized controlled trials (RCTs) involving 319 patients were included. The results of the meta-analyses showed that intracoronary nitroprusside is beneficial in preventing no-reflow/slow-flow, in reducing corrected TIMI frame count, and in improving left ventricular ejection fraction. It also likely reduces adverse reactions in patients after PCI and rehospitalization due to cardiovascular events. However, we must caution that in this review, there is a moderate possibility of bias with regard to patient selection, performance, and publication because of the small number of included studies. A larger sample size and high-quality RCTs are needed for a more reassuring analysis.[7]

**Skrzypczyk P et al.,**Hypertensive crisis is a sudden rise in blood pressure above 99 c. for sex, age and height +5 mm Hg. Depending on patient's symptoms, hypertensive crisis can be divided into hypertensive emergency severe arterial hypertension with target organ insufficiency and/r damage (central nervous system, heart, kidney, eye), and hypertensive urgency - severe arterial hypertension without target organ insufficiency and damage with non-specific symptoms like: headaches, vertigo, nasal bleeding, nausea, and vomiting. The most common causes of hypertensive crisis in neonates and infants are renal artery thrombosis, broncho-pulmonary dysplasia, and coarctation of aorta; in older children - kidney diseases and renal artery stenosis. In neonates and infants symptoms of cardiac failure predominate, whereas in older children symptoms from central nervous system (headaches, nausea, vomiting, changes in level of consciousness, seizures, focal deficits). Hypertensive

crisis is treated with fast- and short-acting medications; 25% reduction of blood pressure within first 8 hours is recommended, with complete normalization within 24-48 hours. Hypertensive emergency should be treated with intravenous agents (labetalol, hydralazine, nicardipine, and sodium nitroprusside), hypertensive urgency with intravenous or oral agents like nifedipine, isradipine, clonidine and minoxidil. Nicardipine is a first-choice medication in neonates.[8]

**Feldstein C et al.,** stated that Hypertensive emergencies are life-threatening conditions because their course is complicated with acute target organ damage. They can present with neurological, renal, cardiovascular, microangiopathic hemolytic anemia, and obstetric complications. After diagnosis, they require the immediate reduction of blood pressure (in <1 hour) with intravenous drugs such as sodium nitroprusside, administered in an intensive care unit. These patients present with a mean arterial pressure >140 mm Hg and grade III to IV retinopathy. Only occasionally do they have hypertensive encephalopathy, reflecting cerebral hyperperfusion, loss of autoregulation, and disruption of the blood-brain barrier. In hypertensive emergencies, blood pressure should be reduced about 10% during the first hour and another 15% gradually over the next 2 to 3 hours to prevent cerebral hypoperfusion. The exception to this management strategy is aortic dissection, for which the target is systolic blood pressure <120 mm Hg after 20 minutes. Oral antihypertensive therapy can usually be instituted after 6 to 12 hours of parenteral therapy. Hypertensive urgencies are severe elevations of blood pressure without evidence of acute and progressive dysfunction of target organs. They demand adequate control of blood pressure within 24 hours to several days with use of orally administered agents. The purpose of this review is to provide a rational approach to hypertensive crisis management.[9]

**Zamami Y et al.,** stated that Recent clinical studies demonstrated that transient postprandial hyperglycemia and hyperinsulinemia may contribute to the development of hypertension. Therefore, we investigated influence of acute hyperglycemia and/or hyperinsulinemia induced by glucose or insulin infusion on neuronal and humoral control of vascular tone in rats. Euglycemic male Wistarrats were pithed under anesthesia and arterial blood pressure was measured. Changes in vascular responses to spinal cord stimulation (SCS) and intravenous bolus injections of noradrenaline, angiotensin II, calcitonin gene-related peptide (CGRP), acetylcholine and sodium nitroprusside (SNP) were studied by infusing various concentration of glucose or insulin. Continuous glucose infusion, which increased both blood glucose and serum insulin levels, significantly augmented adrenergic nerve-mediated pressor

responses to SCS without affecting injection of pressor responses to noradrenaline or angiotensin II. In pithed rats with artificially increased blood pressure and blockade of autonomic outflow, glucose infusion attenuated CGRPergic nerve-depressor responses to SCS without affecting depressor responses to injection of CGRP, acetylcholine or SNP. In pithed rats treated with octreotide, which increased blood glucose without increasing serum insulin levels, glucose infusion caused only significant augmentation of adrenergic nerve-mediated pressor responses. Combined infusion of insulin and glucose, which resulted in increased serum insulin levels with euglycemic, significantly augmented adrenergic nerve-mediated pressor responses and attenuated CGRPergic nerve-mediated depressor responses. The present results suggest that acute hyperglycemia and hyperinsulinemia increases adrenergic nerve-mediated vasoconstriction, which is partly associated with the blunted CGRPergic nerve function, and that plasma insulin concentration associated with hyperglycemia may be responsible for alteration of neuronal vascular regulation.[10]

**Kaplan J .**,Astated thatThe incidence of postoperative hypertension after both cardiac and noncardiac surgery is a major concern. alpha-Adrenergic-blocking drugs, such as phentolamine, and direct-acting vasodilators, such as nitroglycerin and nitroprusside, are commonly used to treat hypertension. Nifedipine, a calcium channel blocker, may also be used, but because no intravenous preparation is available, its effects are not titratable. A new short-acting calcium channel blocker, nicardipine, is a potent vasodilator and produces more selective responses in the coronary versus the systemic vascular circulation. It is an effective cerebral vasodilator, increasing cerebral blood flow and oxygen delivery. Nicardipine can be administered as an intravenous loading infusion of 10 to 15 mg/hr for 25 minutes, followed by a maintenance infusion of 3 to 5 mg/hr. Nicardipine has a short duration factor, is easily titratable and is as effective as nitroglycerin or nitroprusside in the control of hypertension. In summary, nicardipine has many properties of an ideal drug for the treatment of postoperative hypertension.[11]

**Winquist RJ.** Extracts prepared from rat atria, which cause natriuresis and diuresis when injected into bioassay rats, relax aortic smooth muscle preparations. A family of atrial peptides has been isolated, purified and synthesized which elicit similar biological responses as the atrial extracts. The in vitro vasodilator profile of synthetic atrial natriuretic factor (sANF) exhibits many similarities to sodium nitroprusside including inhibition of agonist-induced but not high-K+-induced contractions, relaxation independent of the vascular endothelium and elevation of cyclic GMP in aortic smooth muscle coincident with relaxation.

Aortic rings remain relaxed in the presence of sANF but can be recontracted following a sufficient washout period. sANF causes a significant activation of the particulate (but not soluble) form of guanylate cyclase which is seemingly consistent with the presence of high affinity receptors for sANF in plasma membranes prepared from aortic tissue. Both species and regional vascular differences exist for the vasodilator activity of the synthetic atrial peptides.[12]

**Varon J** .,statedthatApproximately 72 million people in the US experience hypertension. Worldwide, hypertension may affect as many as 1 billion people and be responsible for approximately 7.1 million deaths per year. It is estimated that approximately 1% of patients with hypertension will, at some point, develop a hypertensive crisis. Hypertensive crises are further defined as either hypertensive emergencies or urgencies, depending on the degree of blood pressure elevation and presence of end-organ damage. Immediate reduction in blood pressure is required only in patients with acute end-organ damage (i.e. hypertensive emergency) and requires treatment with a titratable, short-acting, intravenous antihypertensive agent, while severe hypertension without acute end-organ damage (i.e. hypertensive urgency) is usually treated with oral antihypertensive agents. The primary goal of intervention in a hypertensive crisis is to safely reduce blood pressure. The appropriate therapeutic approach of each patient will depend on their clinical presentation. Patients with hypertensive emergencies are best treated in an intensive care unit with titratable, intravenous, hypotensive agents. Rapid-acting intravenous antihypertensive agents are available, including labetalol, esmolol, fenoldopam, nicardipine and sodium nitroprusside.[13]

**WilfriedMullens et al.,** Safety and efficacy of sodium nitroprusside (SNP) for patients with acute decompensated heart failure (ADHF) and low-output states. Inotropic therapy has been predominantly used in the management of patients with ADHF presenting with low cardiac output.In patients with advanced, low-output heart failure, vasodilator therapy used in conjunction with optimal current medical therapy during hospitalization might be associated with favorable long-term clinical outcomes irrespective of inotropic support or renal dysfunction and remains an excellent therapeutic choice in hospitalized ADHF patients.[14]

**Dr. Gisela Gregeraus Mannheim Bonn 2004.et al.,**

Health care products that must be sterile but are unsuitable for terminal sterilisation have to be processed under aseptic conditions. For example, all product parts or components that are in direct contact with aseptically-filled sterile product during the manufacturing process require pre-sterilisation. In addition, production has to take place in a controlled manufacturing environment where microbiological and particulate levels are maintained at defined low levels and where human intervention in the manufacturing process is minimised. In aseptic processing maximum efforts must be expended to use consistently qualified equipment and materials and validated systems, to use adequately trained personnel, and to control the environment. Furthermore a well documented systematic process is needed which impacts risks on product quality using the Hazard Analysis and Critical Control Points (HACCP) concept considering all aspects of qualification of equipment and materials and validation of the process (for example facility design, environment, materials, equipment suitability, supply systems, filter qualification, personnel, incubation conditions for the samples, identification of positive units, demonstration of growth promotion, process validation and quality control). Usually the validation of the whole process is performed by media fill (simulation of the manufacturing process by using nutrient media). A lot of requirements have to be met to ensure that the aseptically manufactured drug product can be regarded as sterile. [15]

**Manoj Sharma Bristol-Myers Squibb.et al**.,Intravenous (IV) administration of many sterile drug products requires admixture preparation using a diluent prior to administration. A pharmaceutical admixture consists of a drug product mixed with an appropriate diluent in a suitable dosing/ delivery device for the purpose of parenteral infusion to the patient. Regulatory agencies, as a part of registration requirements, have listed specifi c requirements for the demonstration of the compatibility of the drug product with the diluents and with the infusion devices.IV admixture studies are an integral part of developing a safe and efficacious sterile drug product intended for IV administration. In this chapter we have listed various challenges and regulatory expectations associated with the IV admixture studies. Although each product may have unique requirements, the general aspects of IV admixture studies remain similar and may be applicable to all sterile products intended for IV administration. We hope that the discussions presented here will help researchers identify critical admixture issues for their products and also gain some insights into addressing those issues.[17]

**Hammer GB** et al.,Sodium nitroprusside is a direct-acting vasodilator used to lower blood pressure in the operating room and ICU. The efficacy of sodium nitroprusside has been analyzed in few pediatric randomized trials. This study assesses the efficacy and safety of sodium nitroprusside following at least 12 hours of IV infusion in children,Sodium nitroprusside is efficacious in maintaining mean arterial blood pressure control in children following a 12-hour infusion. Although a high proportion of patients were found to have elevated cyanide levels, toxicity was not observed..[20]

## AIM AND OBJECTIVE

**AIM**:

The main aim of the present study is to formulate sodium nitroprusside injection 50mg/2ml-2ml,

**OBJECTIVE:**

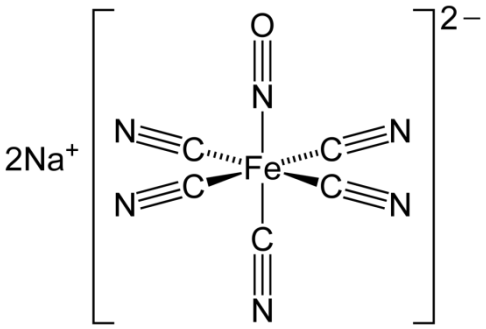
To provide the report for compatibility of Admixture study for **Sodium Nitroprusside Injection 50 mg/2mL-2 mL vial** after admixing with 5% Dextrose injection and results were compared with the US Reference Standard (RS) - NITROPRESS.

**SCOPE:**

To report the Admixture stability study results on physio-chemical parameters, as performed with Exhibit batch samples of **Sodium Nitroprusside Injection 50 mg/2mL-2 mL Vial (**Batch Numbers E0010219, E0010219, E0010319) **and RS - NITROPRESS** (Batch Number 690103F), during Initial time point at 0 hrs and at 24 hrs.

## SODIUM NITRO PRUSSIDE

***STRUCTURAL FORMULA:***




[SODIUM NITRO PRUSSIDE]

Sodium Nitroprusside Injection is not suitable for direct injection.The solution must be further diluted in sterile 5% dextrose injection before infusion.

**DESCRIPTION:**

- Sodium nitroprusside is disodium pentacyanonitrosylferrate(2-) dihydrate, a hypotensive agent whose structural formula is:

- Sodium Nitroprusside, whose molecular formula is $Na_2[Fe(CN)_5NO] \cdot 2H_2O$,
- molecular weight is 297.95.
- Dry sodium nitroprusside is a reddish-brown powder, soluble in water. In an aqueous solution infused intravenously,
- sodiumnitroprusside is a rapid-acting vasodilator, active on both arteries and veins.

- Sodium nitroprusside solution is rapidly degraded by trace contaminants, often with resulting color changes.
- The solution is also sensitive to certain wavelengths of light, and it must be protected from light in clinical use.

- Sodium Nitroprusside Injection is available as:
- 50 mg Fliptop Vial - Each 2 mL vial contains the equivalent of 50 mg sodium nitroprussidedihydrate in sterile water for injection.

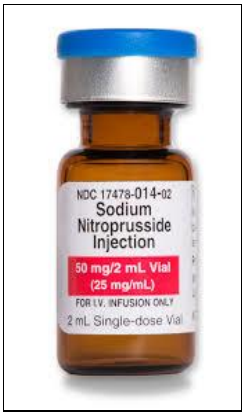
## INDICATIONS:

- Sodium nitroprusside is indicated for the immediate reduction of blood pressure of adult and pediatric patients in hypertensive crises. Concomitant longer-acting antihypertensive medication should be administered so that the duration of treatment with sodiumnitroprusside can be minimized.
- Sodium nitroprusside is also indicated for producing controlled hypotension in order to reduce bleeding during surgery.
- Sodium nitroprusside is also indicated for the treatment of acute congestive heart failure.

## DOSAGE AND ADMINISTRATION

### Dilution to Proper Strength For Infusion:

- Depending on the desired concentration, the solution containing 50 mg of sodium nitroprusside must be further diluted in 250 to 1,000 mL of sterile 5% dextrose injection.
- The diluted solution should be protected from light, using the supplied opaque sleeve, aluminum foil, or other opaque material.
- It is not necessary to cover the infusion drip chamber or the tubing.



**Sodium Nitroprusside injection 2ML**

***STORAGE CONDITIONS:***

- Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]
- Discard solution 24 hours after dilution.
- Protect from light. Retain in carton until time of use.
- Sterile, Nonpyrogenic, Preservative-free.
- The container closure is not made with natural rubber latex.

**SIDE EFFECTS:**

The most important adverse reactions to sodium nitroprusside are the avoidable ones of excessive hypotension and cyanide toxicity, described above under WARNINGS.

The adverse reactions described in this section develop less rapidly and, as it happens, less commonly.

***Methemoglobinemia***

As described in CLINICAL PHARMACOLOGYabove, sodium nitroprusside infusions can cause sequestration of hemoglobin as methemoglobin. The back-conversion process is normally rapid, and clinically significant methemoglobinemia ( > 10%) is seen only rarely in patients receiving Sodium Nitroprusside.

Even patients congenitally incapable of back-converting methemoglobin should demonstrate 10% methemoglobinemia only after they have received about 10 mg/kg of sodium nitroprusside, and a patient receiving sodium nitroprusside at the maximum recommended rate (10 mcg/kg/min) would take over 16 hours to reach this total accumulated dose.

**Overdose:**

Due to its cyanogenic nature, overdose may be particularly dangerous. Treatment of sodium nitroprusside overdose includes the following:

- Discontinuing sodium nitroprusside administration

- Buffering the cyanide by using sodium nitrite to convert haemoglobin to methaemoglobin as much as the patient can safely tolerate
- Infusing sodium thiosulfate to convert the cyanide to thiocyanate.Haemodialysis is ineffective for removing cyanide from the body but it can be used to remove most of the thiocyanate produced from the above procedure.

**MECHANISM OF ACTION:**[33]

- One molecule of sodium nitroprusside is metabolized by combination with hemoglobin to produce one molecule of cyanmethemoglobin and four CN- ions;
- methemoglobin, obtained from hemoglobin, can sequester cyanide as cyanmethemoglobin;
- thiosulfate reacts with cyanide to produce thiocyanate; thiocyanate is eliminated in the urine; cyanide not otherwise removed binds to cytochromes.
- Cyanide ion is normally found in serum; it is derived from dietary substrates and from tobacco smoke.
- Cyanide binds avidly (but reversibly) to ferric ion (Fe+++), most body stores of which are found in erythrocyte methemoglobin (metHgb) and in mitochondrial cytochromes.
- When CN is infused or generated within the bloodstream, essentially all of it is bound to methemoglobin until intraerythrocyticmethemoglobin has been saturated.
- Sodium nitroprusside is further broken down in the circulation to release nitric oxide (NO),
- which activates guanylatecyclase in the vascular smooth muscle.
- This leads to increased production of intracellular cGMP, which stimulates calcium ion movement from the cytoplasm to the endoplasmic reticulum,
- reducing the level of available calcium ions that can bind to calmodulin.
- This ultimately results in vascular smooth muscle relaxation and vessel dilation.

**DETAILED PHARMACOLOGY** :[33]

Human Pharmacology the hypotensive effects of intravenously administered Sodium Nitroprusside are due to peripheral vasodilatation and reduction in peripheral resistance as a result of a direct action on the blood vessel walls, independent of autonomic innervation.

The active component in Sodium Nitroprusside is the free Nitroprusside radical. The evanescent nature of the drug's hypotensive effect is due to the destruction of the active radical.

Infused Sodium Nitroprusside is rapidly distributed to a volume that is approximately coextensive with the extracellular space.

The drug is cleared from this volume by intraerythrocytic reaction with hemoglobin (Hgb), and Sodium Nitroprusside' s resulting circulatory half-life is about two minutes.

**METABOLISM:**

As shown in the diagram below, the essential features of Nitroprusside metabolism are:

- One molecule of Sodium Nitroprusside is metabolized by combination with hemoglobin to produce one molecule of cyanmethemoglobin and four CN- ions;

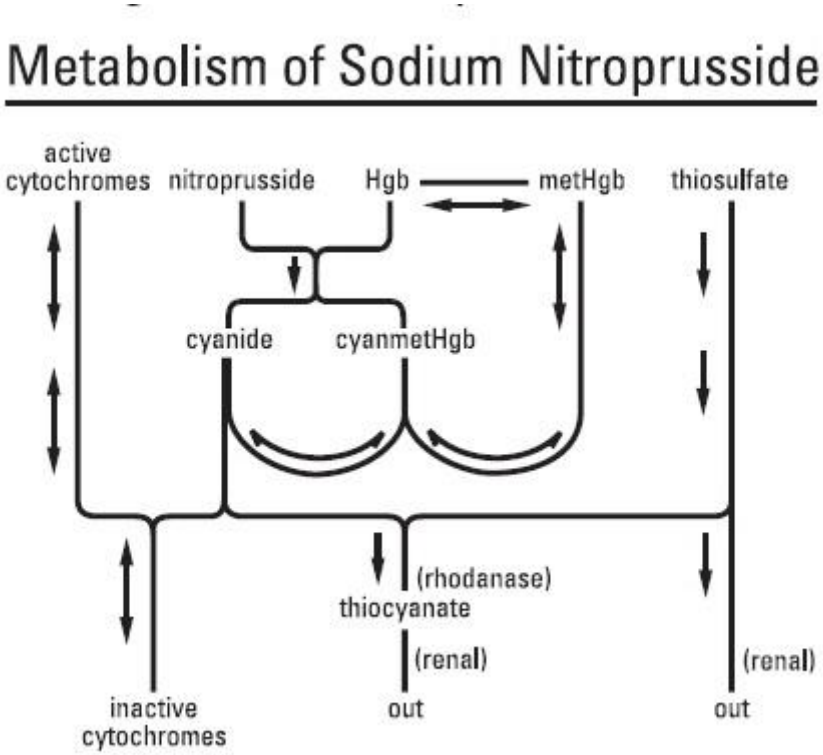
- Methemoglobin, obtained from hemoglobin, can sequester cyanide as cyanmethemoglobin;

- Thiosulfate reacts with cyanide to produce thiocyanate; Thiocyanate is eliminated in the urine.

- Cyanide not otherwise removed binds to cytochromes;

- Cyanide is much more toxic than methemoglobin or thiocyanate.

Cyanide ion is normally found in serum; it is derived from dietary substrates and from tobacco smoke. Cyanide binds avidly (but reversibly) to ferric ion (Fe+++), most body stores of which are found in erythrocyte methemoglobin (metHgb) and in mitochondrial cytochromes. When CN- is infused or generated within the bloodstream, essentially all of it is bound to methemoglobin until intraerythrocyticmethemoglobin has been saturated. When the Fe+++ of cytochromes is bound to cyanide, the cytochromes are unable to participate in oxidative metabolism. In this situation, cells may be able to provide for their energy needs by utilizing anaerobic pathways, but they thereby generate an increasing body burden of lactic acid.




Other cells may be unable to utilize these alternate pathways, and they may die hypoxic deaths. CN- levels in packed erythrocytes are typically less than 1 mmol/L (less than 25 mcg/L);

levels are roughly doubled in heavy smokers. At healthy steady-state, most people have less than 1% of their hemoglobin in the form of methemoglobin.

Nitroprusside metabolism can lead to methemoglobin formation (a) through dissociation of cyanmethemoglobin formed in the original reaction of Sodium Nitroprusside with Hgb and (b) by direct oxidation of Hgb by the released nitroso group.

Relatively large quantities of Sodium Nitroprusside, however, are required to produce significant methemoglobinemia.

At physiologic methemoglobin levels, the CN- binding capacity of packed red cells is a little less than 200 μmol/L (5 mg/L).

Cytochrome toxicity is seen at levels only slightly higher, and death has been reported at levels from 300 to 3,000 μmol/L (8 to 80 mg/L). Put another way, a patient with a normal

red-cell mass (35 mL/kg) and normal methemoglobin levels can buffer about 175 mcg/kg of CN- , corresponding to little less than 500 mcg/kg of infused Sodium Nitroprusside.

Some cyanide is eliminated from the body as expired hydrogen cyanide, but most is enzymatically converted to thiocyanate (SCN- ) by thiosulfate-cyanide sulfur transferase (rhodanase, EC 2.8.1.1), a mitochondrial enzyme.

The enzyme is normally present in great excess, so the reaction is rate-limited by the availability of sulfur donors, especially thiosulphate, cystine and cysteine.

Thiosulfate is a normal constituent of serum, produced from cysteine by way of ßmercaptopyruvate. Physiological levels of thiosulfate are typically about 0.1 mmol/L (11 mg/L), but they are approximately twice this level in children and in adults who are not eating.

Infused thiosulfate is cleared from the body (primarily by the kidneys) with a t½ of about 20 minutes. When thiosulphate is being supplied only by normal physiologic mechanisms, conversion of CNto SCN- generally proceeds at about 1 mcg/kg/min.

The rate of CN- clearance corresponds to steady-state processing of a Sodium Nitroprusside infusion of slightly more than 2 mcg/kg/min.

CN- begins to accumulate when Sodium Nitroprusside infusions exceed this rate. Thiocyanate (SCN- ) is also a normal physiological constituent of serum, with normal levels typically in the range of 50 to 250 μmol/L (3 to 15 mg/L).

Clearance of SCN- is primarily renal, with a t½ of about three days. In renal failure, the t½ can be doubled or tripled. Oral administration of Sodium Nitroprusside does not produce the dramatic decrease in blood pressure seen with intravenous administration.

The effects of chronic oral administration are similar to those obtained with oral potassium thiocyanate. Sodium Nitroprusside for Injection 15 In hypertensive patients, moderate depressor doses of Sodium Nitroprusside induce renal vasodilation roughly equivalent to the decrease in pressure, without an appreciable increase in renal blood flow or a decrease in glomerular filtration. In normotensive subjects, acute reduction of mean arterial pressure to 60-75 mm Hg by infusion of Sodium Nitroprusside caused significant increase in renin activity of renal venous plasma in correlation with a degree of reduction in pressure.

Renal response to reduction in pressure was more striking in renovascular-hypertensive patients, with significant increase in renin release occurring from the involved kidney at mean arterial pressures ranging from 90-137 mm Hg.

Furthermore, the magnitude of renin release from the involved kidney was significantly greater when compared to that in normotensive subjects; while in the contralateral, uninvolved kidney, no significant release of renin was detected during the reduction of pressure.

## DEXTROSE- dextrose injection, solution:[32]

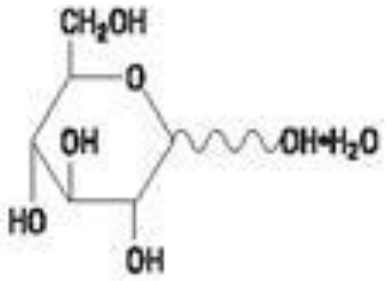
**5% Dextrose Injection USP**

**Partial Fill**

**DESCRIPTION:**

- Each mL of 5% Dextrose Injection USP contains:Hydrous Dextrose USP 50 mg; Water for Injection USP qs,

- pH: 4.5 (3.5–6.5)
  Calculated Osmolarity: 250 mOsmol/liter
  Calories per 100 mL: 17
- This solution is sterile, nonpyrogenic, isotonic and contains no bacteriostatic or antimicrobial agents. This product is intended for intravenous administration.The formula of the active ingredient is:

| **Ingredient** | **Molecular Formula** | **Molecular Weight** |
|---|---|---|
| Hydrous Dextrose USP |  | 198.17 |

## CLINICAL PHARMACOLOGY:

- 5% Dextrose Injection USP provides calories and is a source of water for hydration. It is capable of inducing diuresis depending on the volume administered and the clinical condition of the patient.
- Dextrose is readily metabolized, may decrease losses of body protein and nitrogen, promotes glycogen deposition and decreases or prevents ketosis if sufficient doses are provided.

- Water is an essential constituent of all body tissues and accounts for approximately 70% of total body weight. Average normal adult daily requirements range from two to three liters (1.0 to 1.5 liters each for insensible water loss by perspiration and urine production).

**INDICATIONS AND USAGE:**

5% Dextrose Injection USP is indicated for use in adults and pediatric patients as sources of calories and water for hydration.

This product is designed for use as a diluent and delivery system for intermittent intravenous administration of compatible drug additives. Consult prescribing information for INDICATIONS AND USAGE of drug additives to be administered in this manner.

**CONTRAINDICATIONS:**

Solutions containing dextrose may be contraindicated in patients with hypersensitivity to corn products.

Do not administer 5% Dextrose Injection USP simultaneously with blood through the same infusion set because hemolysis or pseudoaggultination may occur.

**WARNINGS:**

The administration of intravenous solutions can cause fluid and/or solute overload resulting in dilution of serum electrolyte concentrations, overhydration, congested states or pulmonary edema. The risk of dilutional states is inversely proportional to the electrolyte concentrations of administered parenteral solutions.

Prolonged infusion of isotonic or hypotonic dextrose in water may increase the volume of extracellular fluid and cause water intoxication.

Solutions containing dextrose without electrolytes should not be administered simultaneously with blood through the same infusion set because of the possibility of agglomeration.

Excessive administration of potassium-free dextrose solutions may result in significant hypokalemia. Serum potassium levels should be maintained and potassium supplemented as required.

In very low birth weight infants, excessive or rapid administration of dextrose injection may result in increased serum osmolality and possible intracerebral hemorrhage.

**MANUFACTURING PROCESS OF SODIUM NITRO PRUSSIDE INJECTION 50 mg/2ml-2ml :[15]**

| **Product name** | **Strength** | **Batch No.** |
|---|---|---|
| **SODIUM NITROPRUSSIDE INJECTION** | **50mg/2mL - 2mL** | E0010119 |
| | | E0010219 |
| | | E0010319 |

**DRUG PRODUCT**

Sodium Nitroprusside Injection USP 50mg/2mL - 2 mL

(Batch No: E0010119, E0010219& E0010319) with batch size of 30 L were manufactured at Caplinsteriles limited.

Limited Unit IV to provide documents for regulatory filing, provide samples for the stability program and to demonstrate that the critical parameters established in the process are suitable to manufacture a product that meets established specifications.

Formulation of sodium nitroprusside injection 50mg/2ml-2ml is an aseptic filling process,

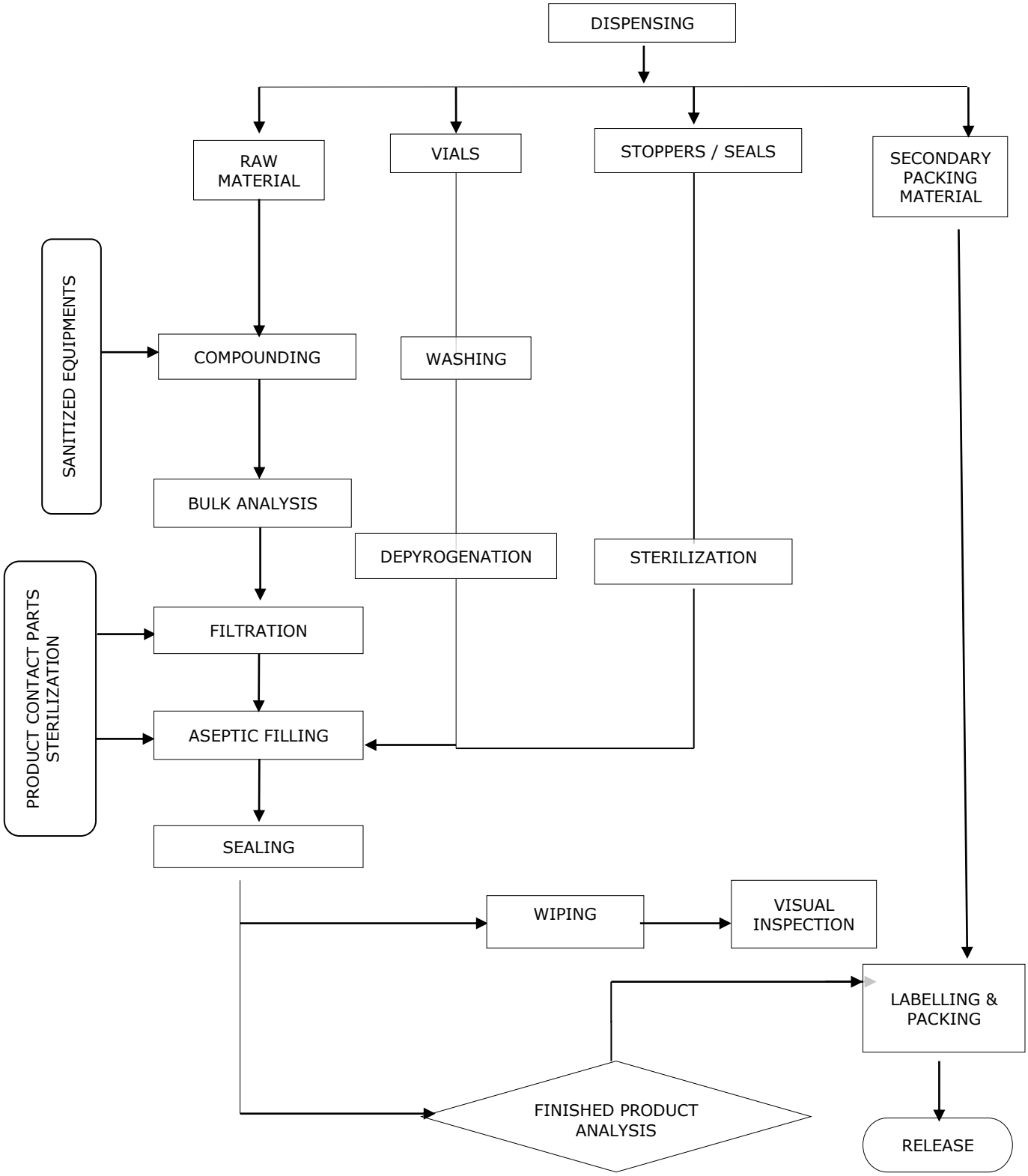
**ASEPTIC PROCESSING:**[16] In an aseptic filling process, the drug product, containers and closures are sterilized separately and then brought together under an extremely high quality environmental condition designed to reduce the possibility of a non-sterile unit. Aseptic processing involves more variables than terminal sterilization.

**Sterility**:[15]

Sterility1, 2 means the complete absence of any viable microorganism in a drug product. The specification of sterility is unchanging and is independent of the kind of manufacturing process: sterilization of the final product in its container closure system or aseptic manufacturing.

| | | | |
|---|---|---|---|
| **Generic Name** | Sodium Nitroprusside Injection USP 50mg/2mL-2mL | | |
| **Pharmacopeial status** | USP | | |
| **Label Claim** | Each vial contains sodium nitroprusside 50mg/2mL | | |
| **Target Fill volume** | 2.20 mL (2.15 mL – 2.25 mL) | | |
| **Category** | Vasodilator | | |
| **Batch Numbers of Drug Products for ANDA submission** | I | II | III |
| | E0010119 | E0010219 | E0010319 |
| **Date of Manufacturing** | 01/2019 | 02/2019 | 03/2019 |
| **Batch Size** | 30 Liters | | |
| **Storage condition** | Store at 20 ºC – 25 ºC (68 º F - 77ºF), (USP controlled room temperature). Protect from light, it should be stored in its carton until it is used. | | |
| **Drug Product Manufacturer** | CaplinsterilesLimited<br>Unit IV, Guruvarajakandigai, Gummidipoondi. | | |
| **Any additional information in label** | Potent drug: Monitor blood pressure before and during administration.<br>Not for direct injection.<br>Protect solution and intravenous infusion from light.<br>Discard solution after 24 hours dilution. | | |
| **Proposed standard packaging of the product** | Each vial should be labelled (Sticker label) such labelled vials are inserted in to mono carton along with light protective sleeve (Kept in a card board pouch) and leaflet. | | |
| **Mode of Administration** | IV | | |

## MANUFACTURING SCHEMATIC REPRESENTATION:



## BATCH MANUFACTURING PROCESS:

- Raw materials dispensed as per BMR Batch manufacturing record,fromwarhouse department.
- Primary packing materials like vials, stoppers, seals, filters and Tubings dispensed as per BMR Batch manufacturing record,
- Raw materials sent for compounding process as per BMR.
- Dispensed quantity Vials sent for decartining,
- Decartoning is process by which dispensed quantity of vials visually checked and good vials sent for vial washing,
- Activate the pneumatic mechanism such that the platform is raised slightly above the level of the inspection station.
- Transfer the vials manually by pushing with the stainless steel plate to the inspection station.Inspect the vials for any defects

- Cracks,
- Moulded defect,
- Scraches on vials,
- Stain,
- Colour defect,
- Vial neck damage,like, Moulding, Vial neck, Crack/Broken defects, and Black and Brown spot. and keep the defective vials in the rejected trays.

- Push the good inspected vials in to the plastic tray and load these vials in vial washing machine.
- Count the rejected vials and enter the rejected vials in Batch Production Record.
- Record the operation details in Batch production record.
- After completion of decartoning process good vials sent for the vial washing
- Vials are washed as per BMR requirement.
- Vials were washed and depyrogenated and reached for filling station for aseptic manufacturing process.
- Stoppers and seals subjected for the decartoning process, inspect stoppers and seals for any defects like
- Damage of issued stopper cover,
- Damage of issued seals cover,

- Any discrepencies observed in that bags total entire bags of stoppers and seals sent for destruction.

- Stoppers and seals were subjected for sterilization process.
- Sterilization:
- Stoppers, seals, vial filling machine parts, subjected for sterilization process,**122 º C for 30 mins.**
- Bulk compounding process, as per BMR.
- Check the light intensity less than 20 LUX.
- Sterile filtration process through 0.2 micron filter.
- Aseptic filling process. (2ml fill)
- Stoppering and sealing process.
- After aseptic filling process the vials are sent for wiping and visual inspection process
- During visual inspection vials were visually inspected by qualified visual inspectors, vials observed any defects they may catergories into
  - Critical defects
  - Major defects
  - Minor defects
- **Critical defects includes**:

- Crack/broken,
- Partial sealing,
- Discolouration,

- **Major defects includes:**

- White particles
- Black/brown particles
- Fibres

- **Minor defects includes:**

- Cosmectic defects,
- Moulded defects / scratches,

- If any defects observed during visual inspection , that vials are sent for the destruction and destructed vials were recorded in the BMR.
- After visual inspection the good vials are sent for the labelling and packaing.
- Finally the labelled and packed vials sent for the finished product storage.

# LIST OF EQUIPMENT USED:

| **COMPOUNDING & FILTERATION** | | |
|---|---|---|
| **S.No.** | **Name of equipment & capacity** | **Equipment Id** |
| 01 | Manufacturing reactor 50L | CP4/PI/015 |
| 02 | Pressure vessel | CP4/PI/245 |
| 03 | Pressure vessel | CP4/PI/246 |
| **FILLING** | | |
| 01 | FILLING MACHINE ID NO (80-140vials/min) | CP4/PI/003 |
| 02 | SEALING MACHINE ID NO (80-140vials/min) | CP4/PI/004 |
| **VIAL WASHING & DEPYROGENATION** | | |
| 01 | Automatic High Speed Linear Vial Washing Machine | CP4/PI/001 |
| 02 | Vial Sterilizing and Depyrogenation Tunnel | CP4/PI/002 |
| **AUTOCLAVE** | | |
| 01 | HPHV Steam sterilizer | CP4/PI/009 v |
| **INPROCESS** | | |
| **01** | WEIGHING BALANCE | CP4/PI/057 |
| **02** | CCIT APPARATUS | CP4/PI/089 |
| **03** | VISUAL INSPECTION LUX METER | CP4/PI/099 |

| **RAW MATERIAL** | | | | | |
|---|---|---|---|---|---|
| **Ingredients** | **Quantity/ Vial** | **Quantity / Batch** | **Product Batch No.** | **AR. Number** | **Manufactured By** |
| Sodium Nitroprusside, USP **(Item code: RM/00181)** | 50 mg | 750.0 g | E0010119 | QC/RM/16/0070 | AzicoBiophore |
| | | | E0010219 | QC/RM/16/0071 | |
| | | | E0010319 | QC/RM/16/0072 | |
| Water for injection, USP/BP | q.s. to 2.0 mL | q.s. to 30.0 L | E0010119 | QC/IP/17/0010 | CPLL, unit IV |
| | | | E0010219 | QC/IP/17/0025 | |
| | | | E0010319 | QC/IP/17/0039 | |

Raw materials were dispensed as per BMR by warhouse department.

Sodium nitroprusside USP(API),as per BMR requirement quantity was dispensed from warhouse department**.**

Dispensed quantity measured and recorded in respective BMR.

| **CONSUMABLES** | | | |
|---|---|---|---|
| **Tubing's** | | | |
| **Item** | **Product Batch No.** | **AR. Number** | **Manufactured By** |
| Pharmapure low spallations pump tubing. Part code No: AL242017 ID: 1/4, OD: 3/8, Wall 1/16.<br>**Item code: CM/00023** | E0010119 | QC/MI/16/0188 | Saint Gobain |
| | E0010219 | QC/MI/16/0194 & QC/MI/16/0195 | |
| | E0010319 | QC/MI/16/0195 & QC/MI/16/0333 | |
| Pharmapure pure silicon tubing, Part code No: AL242029, ID 3/8 X OD 5 / 8 X WALL 1/ 8.<br>**Item code: CM/00025** | E0010119 | QC/MI/16/0073 | Saint Gobain |
| | E0010219 | | |
| | E0010319 | | |

Consumables like filling tubing's were dispensed by Warhouse Department,

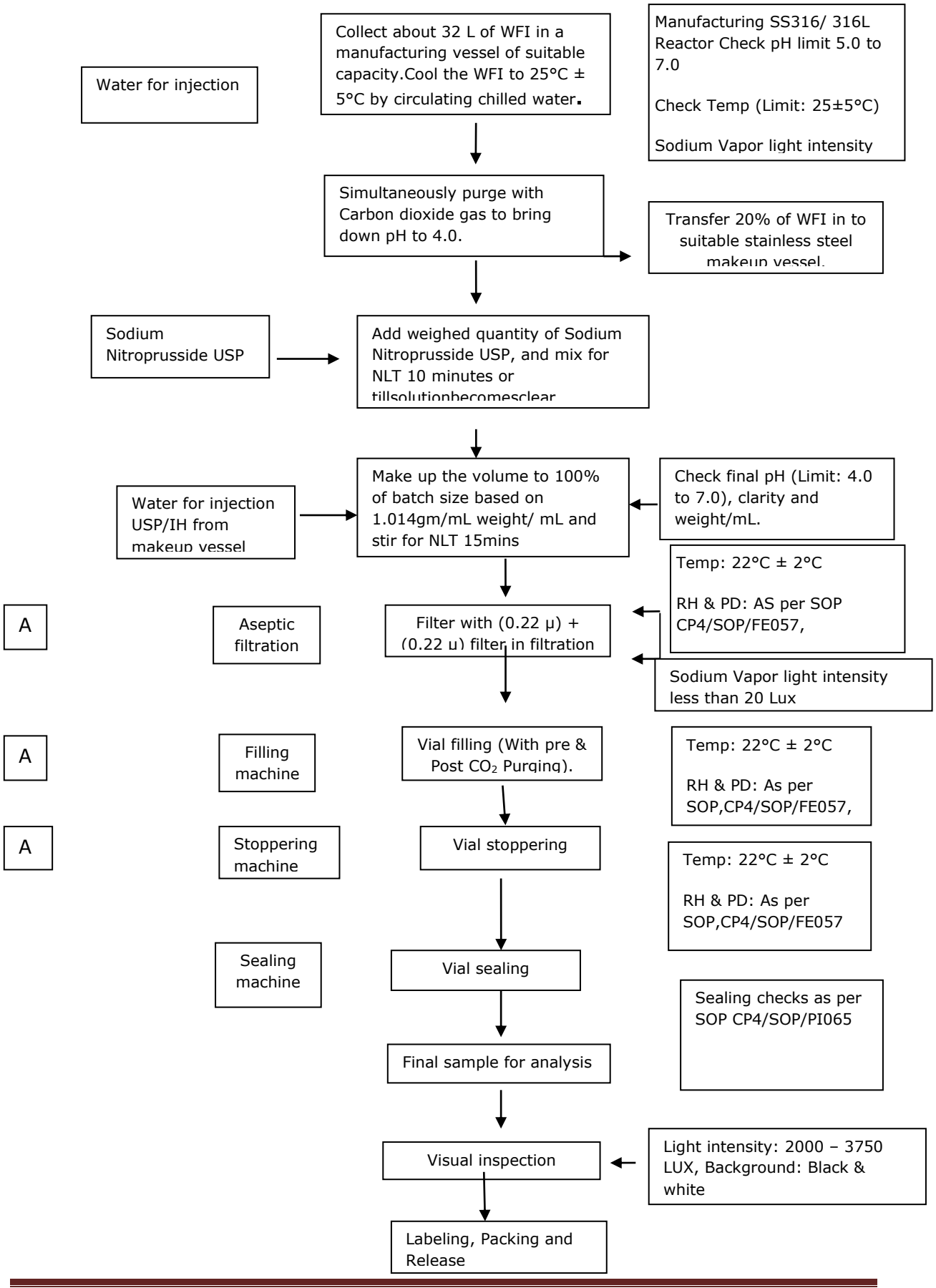
Dispensed quantity measured and recorded in respective BMR.

**PRIMARY PACKING MATERIALS:**

| Item | Quantity / Batch in nos | Product Batch No. | AR. Number | Manufactured By |
|---|---|---|---|---|
| 2 mL/13 mm Dark Amber Fiolax Tubular Vials (USP Type-I).<br>**(Item code: PM/00172)** | 14318 | E0010119<br>E0010219<br>E0010319 | QC/PM/16/0162 | Schott Kaisha |
| 13 mm Dark Grey Bromobutyl stoppers with silicate filler V9145 FM257/2 (Ready to sterilize)<br>**(Item code: PM/00166)** | 15000 | E0010119<br>E0010219<br>E0010319 | QC/PM/16/0153 | Datwyler |
| 13 mm Dark green DG01 Flip off seals<br>**(Item code: PM/00292)** | 15000 | E0010119<br>E0010219<br>E0010319 | QC/PM/16/0194 | Adit Pharma |

| **Filters used for product manufacturing** | | | |
|---|---|---|---|
| **Item** | **Product Batch No.** | **AR. Number** | **Manufactured By** |
| 0.2µ PES capsule filter,<br>Catalogue No: 5445307H8-00<br>**Item code: CM/00045** | E0010119<br>E0010219<br>E0010319 | QC/MI/16/0377<br>QC/MI/16/0451 | Sartorius |

**PROCESS FLOW:**



**BULK COMPOUNDING PROCESS:**

- Collect about 32 L of WFI in a manufacturing vessel of suitable capacity.
- Cool the WFI to 20-25º C by circulating brain chilled water.
- Check the temperature: 20-25 º C.
- Sodium vapour light intensity less than 20 Lux.
- Simultaneously purge with CO2 gas bring down PH to 4.
- Transfer 20% of WFI in to a suitable stainless steel make up vessel.
- Add weighed quantity of sodium nitro prusside USP, and mix for NLT 10 mins or stirr the solution till becomes clear.
- Make up the volume to 100% of batch based on 1.014 gm/ml.stirr for 15 mins.
- The following Table summarizes the actual process parameter and observation During bulk manufacturing process.

**EXPERIMENTAL RESULTS AND TABLES:**

**Table 01:(COMPOUNDING PROCESS )**

| Ingredient | Actual | Observation | | |
|---|---|---|---|---|
| | | E0010119 | E0010219 | E0010319 |
| Total WFI collected | 31.904 kg | 32.9 kg | 32.6 kg | 32.6 kg |
| Temperature of WFI | NLT 80°C | 80.6 | 80.4 | 82.2 |

**Table :02 ( during compounding process)**

| Ingredient | Actual | Observation | | |
|---|---|---|---|---|
| | | E0010119 | E0010219 | E0010319 |
| pH | 5 to 7 | 5.86 | 5.96 | 5.58 |
| Conductivity | NMT 1.3 | 0.62 | 0.71 | 0.69 |
| TOC | 550 ppb | 33 | 37.8 | 70.5 |
| pH of WFI after purging with carbon – dioxide gas | 4.00 | 4.03 | 4.04 | 4.04 |
| Sodium vapor lamp intensity | less than 20 lux | 15 | 12 | 10 |
| Mixing time and RPM after addition of sodium nitroprusside | 10 min/250 RPM | 10 min/250 RPM | 10 min/250 RPM | 10 min/250 RPM |
| Mixing time and RPM after final volume make up | 15 min/250 RPM | 15 min/250 RPM | 15 min/250 RPM | 15 min/250 RPM |

**Discussion:**

During the compounding (95% volume make up) the sample were collected and sent for QC, reports of the data's described above in table 02.

**TABLE :03**

**Inprocess Bulk solution test results: (After 100% volume mack up)**

| Test | spec limit | Observation | | |
|---|---|---|---|---|
| | | **E0010119** | **E0010219** | **E0010319** |
| pH | 4 to 7 | 4.05 | 4.08 | 4.43 |
| Weight/mL | 0.9971-1.0376 | 1.004 g/mL | 1.005 g/mL | 1.013g/mL |
| Assay (%w/w) | 95.0 to 105.0 | 99.1% | 98.4% | 100% |

**Remarks:** Inprocess Bulk solution test results of all the 3 batches meets the acceptance criteria

**Filtration:**

Solution was filtered aseptically using sterilized 0.2 µ filter connected under the laminar flow in filtration room using Carbon – dioxide as a processing gas.

Filtration pressure limit and observation are provided below

| Batch No | Filtration pressure Limit | Observation |
|---|---|---|
| E0010119 | 1.0 to 2.0 Kg/ sq. cm | 1.0 kg/sq.cm |
| E0010219 | 1.0 to 2.0 Kg/ sq. cm | 1.0 kg/sq.cm |
| E0010319 | 1.0 to 2.0 Kg/ sq. cm | 1.0 kg/sq.cm |

**Filter Integrity**: During the manufacturing of submission batches (Batch No:E0010119, E0010219 & E0010319)pre-filtration (using WFI) and post-filtration (using product solution) integrity of the filters were tested. Refer Table 2 for results of pre & post integrity testing results for Filters

**Pre & Post Filtration Integrity Testing Results for filters:**

**TABLE :04**

**(B. No.: E0010119)**

| Filter.Cat No. 5445307H8-00 | Water BubblePoint Pressure 46.4 PSI(Pre-filtration) | Product SolutionBubble Point PressureNLT46.4 PSI(Post-filtration) |
|---|---|---|
| S.No: 65, Lot No. 623000303 | 60.3PSI | 55.7 PSI |
| S.No: 135, Lot No. 623000303 | 59.8PSI | 63.4 PSI |

**TABLE :05**

**(B. No.: E0010219)**

| Filter.Cat No. 5445307H8-00 | Water BubblePoint Pressure 46.4 PSI(Pre-filtration) | Product SolutionBubble Point PressureNLT46.4 PSI(Post-filtration) |
|---|---|---|
| S.No: 98, Lot No. 623000303 | 58.1 PSI | 55.9 PSI |
| S.No: 138, Lot No. 623000303 | 59.3 PSI | 60.4 PSI |

**TABLE :06**

**(B. No.: E0010319)**

| Filter.Cat No. 5445307H8-00 | Water BubblePoint Pressure 46.4 PSI(Pre-filtration) | Product SolutionBubblePoint PressureNLT46.4 PSI(Post-filtration) |
|---|---|---|
| S.No: 200, Lot No. 623000303 | 59.2 PSI | 59.9PSI |
| S.No:150, Lot No. 623000303 | 59.1 PSI | 57.3 PSI |

**Remarks :**

All the submission batches results of pre and post-filtration filter integrity testing complies with in the limits.

**Bulk solution testing after passing through 0.2µ filter before final filtration:**Sample for analysis was collected at end of 1st filtration. The results of the analysis samples are presented below.

**TABLE:07**

| TEST | Specification | Batch Numbers | | |
|---|---|---|---|---|
| | | **E0010119** | **E0010219** | **E0010319** |
| Bioburden | Not more than 10 cfu/100 mL | Nil | Nil | Nil |
| Bacterial Endotoxins Test (USP Endotoxin Units/mg of Sodium Nitroprusside) | Not more than 8.3 EU/mg | Less than1.038 | Less than1.038 | Less than1.038 I |

**Remarks :**All the submission batches results of Bulk solution testing after passing through 0.2µ filter before final filtration:Sample for analysis was collected at end of 1stfiltrationtesting complies with in the limits.

**Filling and Sealing:**

The items required for filling have been washed & sterilized as per the Filling BMR and respective SOPs.

The parameters for washing, sterilization of vials were set as per the Filling BMR and respective SOPs.

System Flush Study:

System flush study was performed to clear and condition the tubing, and filling line components. Refer Table 3 for System Flush Study Results

**System Flush Study Results:TABLE : 08System Flush Samples of 1, 2, 3 & 4 strokes 32 vials samples**

| Test | Specification | E0010119 | E0010219 | E0010319 |
|---|---|---|---|---|
| Description | A clear, reddish brown color solution, free from visible particles. | A clear, reddish brown color solution,freefromvisibleparticles. | A clear, reddish brown color solution, free from visible particles. | A clear, reddish brown color solution, free from visible particles. |
| pH | 4.0 to 7.0 | 4.25 | 4.27 | 4.40 |
| Assay<br>Each 2mL contains Sodium Nitroprusside in mg % Labeled amount | 93.0 to 107.0%<br>46.5 to 53.5mg/2mL | 98.2%<br>49.122 mg/2mL | 98.1%<br>49.037 mg/2mL | 99.7%<br>49.847 mg/2mL |

**TABLE : 09System Flush Samples of 5, 6, 7 & 8 strokes 32 vials samples**

| Test | Specification | E0010119 | E0010219 | E0010319 |
|---|---|---|---|---|
| Description | A clear, reddish brown color solution, free from visible particles. | A clear, reddish brown color solution, free from visible particles. | A clear, reddish brown color solution, free from visible particles. | A clear, reddish brown color solution, free from visible particles. |
| pH | 4.0 to 7.0 | 4.23 | 4.24 | 4.42 |
| AssayEach 2mL contains Sodium Nitroprusside in mg % Labeled | 93.0 to 107.0 %<br>46.5 to 53.5 mg/2mL | 98.3%<br>49.152 mg/2mL | 98.3 %<br>49.144 mg/2mL | 99.8%<br>49.891 mg/2mL |

| | | | | |
|---|---|---|---|---|
| amount | | | | |

**TABLE : 10 9, 10, 11 & 12 strokes 32 vials samples**

| Test | Specification | E0010119 | E0010219 | E0010319 |
|---|---|---|---|---|
| Description | A clear, reddish brown color solution, free from visible particles. | A clear, reddish brown color solution, free from visible particles. | A clear, reddish brown color solution, free from visible particles. | A clear, reddish brown color solution, free from visible particles. |
| pH | 4.0 to 7.0 | 4.21 | 4.22 | 4.35 |
| AssayEach 2mL contains Sodium Nitroprusside in mg % Labeled Amount | 93.0 to 107.0 %<br>46.5 to 53.5 mg/2mL | 98.0%<br>49.011 mg/2mL | 98.3%<br>49.125 mg/2mL | 99.7%<br>49.874 mg/2mL |

**DISCUSSION:**

**Remarks:** Results obtained on collected system flush samples were in line with the set In process specification, indicating that the flush volume of solution required to condition the filling line components after production line set up volume of approximately 220 mL is sufficient to condition the system to be within the specified limits.

**Product uniformity at the beginning, middle and end of filling:**

During the filling (Batch No. E0010119, E0010219 & E0010319) samples were collected at beginning, middle and end of filling to evaluate the product uniformity throughout the filling process. Refer Table 4 for Product uniformity test results at the beginning, middle and end of filling.

**TABLE : 11Product uniformity test results at the beginning, middle and end of filling:**

| Test | Specification | E0010119 | | | E0010219 | | | E0010319 | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | **Beginning** | **Middle** | **End** | **Beginning** | **Middle** | **End** | **Beginning** | **Middle** | **End** |
| Description | A clear, reddishbrowncolorsolution, freefromvisibleparticles. | A clear, reddish brown color solution, free from visible particles. | A clear, reddish brown color solution, free from visible particles. | A clear, reddish brown color solution, free from visible particles. | A clear, reddish brown color solution, free from visible particles. | A clear, reddish brown color solution, free from visible particles. | A clear, reddish brown color solution, free from visible particles. | A clear, reddish brown color solution, free from visible particles. | A clear, reddish brown color solution, free from visible particles. | A clear, reddish brown color solution, free from visible particles |
| pH | 4.0 to 7.0 | 4.22 | 4.19 | 4.18 | 4.35 | 4.27 | 4.25 | 4.41 | 4.28 | 4.32 |

| Test | Specification | | E0010119 | | | E0010219 | | | E0010319 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Beginning | Middle | End | Beginning | Middle | End | Beginning | Middle | End |
| AssayEach 2mL contains Sodium Nitroprusside in mg % Labeled Amount | 93.0 to 107.0 %<br>46.5 to 53.5 mg/2mL | 98.6 %<br>49.301 mg/2mL | 98.6 %<br>49.301 mg/2mL | 98.3 %<br>49.166 mg/2mL | 98.3 %<br>49.159 mg/2mL | 98.4 %<br>49.221 mg/2mL | 98.4 %<br>49.185 mg/2mL | 99.7 %<br>49.860 mg/2mL | 100.0 %<br>50.004 mg/2mL | | 100.0 %<br>50.008 mg/2mL |
| **Related Substances** | | | | | | | | | | | |
| Ferrocyanide | Not more than 0.04% | Not Detected | Not Detected | Not Detected | Not Detected | Not Detected | Not Detected | Not Detected | Not Detected | | Not Detected |
| Ferricyanide | Notmore than 0.04% | BDL | BDL | BDL | BDL | BDL | BDL | BDL | BDL | | BDL |

**DISCUSSION:**Product uniformity at the beginning, middle and end of filling Samples were collected and analysed, testing complies with in the limits

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**VISUAL INSPECTION AFTER SEALING:**

After completion of sealing submission batches samples (Batch No. E0010119, E0010219 & E0010319) were subjected to 100% manual Visual inspection and inspected good quantities were again subjected to AQL as described in the Packing Batch Production and Control Record (BMR) and found within the acceptance criteria.

Details of the visual inspection are presented in Table

Details of Visual Inspection**TABLE : 12**

| Description | E0010119 | E0010219 | E0010319 |
|---|---|---|---|
| Total units taken for Visual inspection | 11563 | 11727 | 10407 |
| Rejects during Visual inspection | 628 | 371 | 158 |
| Good qty. transferred to Packing | 10935 | 11356 | 10249 |

**Table:13**

**RESULTS OF UNFILTERED AND FILTERED BULK SOLUTION:**

| Test | Specification | Unfiltered solution | | Fi |
|---|---|---|---|---|
| | | 12 Hrs | 24 Hrs | 24 Hrs |
| Description | A clear, reddish brown color solution, free from visible particles. | A clear, reddish brown color solution, free from visible particles. | A clear, reddish brown color solution, free from visible particles. | A clear, redd brown colo solution, free visible partic |
| pH | 4.0 to 7.0 | 4.2 | 4.15 | 4.62 |
| Assay<br>Each 2mL contains Sodium Nitroprusside in mg % Labeled Amount | 93.0 to 107.0%<br>46.5 to 53.5 mg/2mL | 99.9%<br>49.966 mg/2mL | 100.1%<br>50.030<br>mg/2 mL | 99.8%<br>49.900 mg/2 |

| | | | | | |
|---|---|---|---|---|---|
| **Related Substances** | | | | | |
| Ferrocyanide | Not more than 0.04% | BDL | BDL | BDL | BDL |
| Ferricyanide | Not more than 0.04% | NotDetected | Not Detected | NotDetected | NotDetected |
| Any unspecified Impurity | Not more than 0.2% | BDL | BDL | BDL | BDL |
| Sum of unspecified impurities | Not more than 1.0% | BDL | BDL | BDL | BDL |
| **Color of the solution (by spectrocolorimeter)** | | | | | |
| L | Report the resulted value | 79.12 | 78.85 | 78.81 | 78.98 |
| A | | 11.60 | 11.36 | 10.82 | 10.84 |
| B | | 39.6 | 40.05 | 39.75 | 39.82 |
| Bioburden | Not more than 10 cfu/100 mL | NA | NA | NA | Nillcfu/100 m |
| Bacterial Endotoxins Test (USP | Not more | NA | NA | NA | Less than |

| | | | | | |
|---|---|---|---|---|---|
| Endotoxin Units/mg of Sodium Nitroprusside) | than 8.3 EU/mg | | | | 1.038 EU/mg |

**DISCUSSION:**

NA: Not applicable, BDL: Below Detection Limit.

Remarks: Hold study results of unfiltered and filtered bulk solution from SS 316L vessel meets the acceptance criteria.

**Product Yield at various stages:**

**TABLE : 14**

**Product Yield at various stages**

| S. No. | Description | E0010119 | E0010219 | E0010319 |
|---|---|---|---|---|
| **1** | %Yield after compounding | 98.22 % | 98.22 % | 97.16 % |
| **2** | % Yield after Filtration | 97.22 % | 97.22 % | 96.17% |
| **3** | Batch yield | 80.51 % | 83.84% | 75.34% |
| **4** | Packing yield | 79.91% | 83.24% | 74.73% |

**DISCUSSION:**

Sodium nitroprusside injection 50 mg/2ml-2 ml were formulated and product yield at various stages were described above in table 14,

TABLE:15

STABILITY RESULTS FOR FINISHED PRODUCT:

| TEST | SPECIFICATION | E0010119 | E0010219 |
|---|---|---|---|
| Description | A clear, reddish brown color solution, free from visible particles. | A clear, reddish brown color solution, free from visible particles. | A clear, reddish brow solution, free from v particles. |
| | | Identification | |
| i) By HPLC DAD/UV | The Retention time of the major peak of the sample solution corresponds to that of the standard solution, as obtained in the Assay | The Retention time of the major peak of the sample solution corresponds to that of the standard solution, as obtained in the Assay | The Retention time of major peak of the sam solution corresponds t the standard solution, obtained in the Assay |
| ii) By HPLC DAD | The UV spectrum of the sodium nitroprusside peak of the sample solution corresponds to that of the standard solution, as obtained in the Assay | The UV spectrum of the sodium nitroprusside peak of the sample solution corresponds to that of the standard solution, as obtained in the Assay | The UV spectrum sodium nitroprusside the sample corresponds to that standard solution, as in the Assay |
| | | | |
| Sterility | Should be Sterile | Sterile | Sterile |

| | | | |
|---|---|---|---|
| **Particulate Matter** | | | |
| Visible particles | Free from foreign matter. | Free from foreign matter. | Free |
| **Sub Visible Particles (Number of particles per vial by light obscuration me** | | | |
| ≥10 µm | Not more than 6000 particles per container | 3 particles per container | 5 p c |
| ≥25 µm | Not more than 600 particles per container | 0 particles per container | 0 p c |
| Volume in 5 containers | Not less than10 mL | 10.5 mL | 1 |
| **Related Substances: Method - 1 (%w/w by HPLC):** | | | |
| i) Ferrocyanide $ | Not more than 0.04% | Below detection limit | Below |
| ii) Any unspecified Impurity | Not more than 0.2% | Below detection limit | Below |
| iii) Sum of unspecified impurities | Not more than 1.0% | Below detection limit | Below |
| Ferricyanide $ | Not more than 0.04% | Not detected | Not det |

**PROCEDURE :**

Specification reference: CP4/SPC/QC/MS032-00
Analytical Method Reference: CP4/STP/QC/MS031

**General Admixed Procedure and Precautions:**

Procedure: For admixture study samples preparation, sterile needle and BD syringe (Without silicon) were used for dilution of the dextrose injection. The volume of infusion bags for 250 mL and 1000 mL 5% dextrose injection were measured and approximately overages were found 8% for 250 mL 5% dextrose injection and 5% for 1000 mL 5% dextrose injection.
Precaution: Analysis was performed under sodium light.

**PREPARATION OF ADMIXING SOLUTIONS :**

**Generic product Admixed Sample Solution-1 : (1 Vial in 250 mL 5% Dextrose infusion bag):**

Using 5mL dry syringe (BD Syringe), completely removed the contents from 1 vial of Sodium nitroprusside injection, 50 mg/2 mL (sample from 0 time point of stability study protocol CP4/AM-P/17/063) and injected the entire content of the sample in to a 250 mL of 5% Dextrose bag through injection port. Mixed the contents by shaking the infusion bag horizontally for 1 minute. Admix similarly for all three exhibit batch samples.

**Generic product Admixed Sample Solution-2: (1 Vial in 1000mL 5% Dextrose infusion bag):**

Using 5mL dry syringe (BD Syringe), completely removed the contents from 1 vial of Sodium nitroprusside injection, 50 mg/2 mL (sample from 0 time point of stability study protocol CP4/AM-P/17/063) and injected the entire content of the sample in to a 1000 mL of 5% Dextrose bag through injection port. Mixed the contents by shaking the infusion bag horizontally for 1 minute. Admix similarly for all three exhibit batch samples.

**RS Admixed Sample Solution-1 : (1 Vial in 250 mL 5% Dextrose infusion bag):**

Using 5mL dry syringe (BD Syringe), completely removed the contents from 1 vial of **RS - NITROPRESS** (Sodium nitroprusside injection, 50 mg/2 mL )(sample from 0 time point of stability study protocol CP4/AM-P/17/064) and injected the entire content of the sample in to a 250 mL of 5% Dextrose bag through injection port. Mix the contents by shaking the infusion bag horizontally for 1 minute.

**RS Admixed Sample Solution-2: (1 Vial in 1000mL 5% Dextrose infusion bag):**

Using 5mL dry syringe (BD Syringe), completely removed the contents from 1 vial of **RS - NITROPRESS** (Sodium nitroprusside injection, 50 mg/2 mL )(sample from 0 time point of stability study protocol CP4/AM-P/17/064) and injected the entire content of the sample in to a 1000 mL of 5% Dextrose bag through injection port. Mix the contents by shaking the infusion bag horizontally for 1 minute.

**RESULTS:**

**SODIUM NITROPRUSSIDE INJECTION 50 mg/2mL-2 mL vial,**

**BATCH NO: E0010119 IN SOLUTION 1 AND SOLUTION 2**

**TABLE: 16**

| S.No. | Parameter | Acceptance criteria | | Results obtained | | | |
|---|---|---|---|---|---|---|---|
| | | | | **SOLUTION 1 (1 Vial in 250 mL 5% Dextrose infusion bag)** | | **SOLUTION 2 (1 Vial in 1000mL 5% Dextrose infusion bag)** | |
| | | | | **0 Hour** | **24 Hours** | **0 Hour** | **24 Hour** |
| 1. | Description | Clear Colourless Solution, free from visible particles. | | Clear Colourless Solution, free from visible particles. | Clear Colourless Solution, free from visible particles. | Clear Colourless Solution, free from visible particles. | Clear Colourless Solution, free from visible particles. |
| 2. | pH | Between 3.5 and 6.0 | | 4.68 | 4.57 | 4.53 | 4.45 |
| 3. | Assay by HPLC | 90.0% to 110.0% | | 98.1% | 98.4% | 99.0% | 100.3% |
| 4. | Related substances by HPLC | a) Ferrocyanide | Not more than 0.04% | Not Detected | Not Detected | Not Detected | Not Detected |
| | | b) Any unspecified impurity | Not more than 0.2% | Not Detected | Not Detected | Not Detected | Not Detected |
| | | c) Total impurities | Not more than 1.0% | Not Detected | Not Detected | Not Detected | Not Detected |

**DISCUSSION**:

sodium nitroprusside injection 50 mg/2ml-2 ml vial,

batch no: E0010119 in solution 1 and solution 2 results of the data's were collected,

As its meets the acceptance criteria.

**RESULTS**

**SODIUM NITROPRUSSIDE INJECTION 50 mg/2mL-2 mL vial,**
**BATCH NO: E0010219 IN SOLUTION 1 AND SOLUTION 2**

**TABLE: 17**

| S.No. | Parameter | Acceptance criteria | | Results obtained | | | |
|---|---|---|---|---|---|---|---|
| | | | | SOLUTION 1 (1 Vial in 250 mL 5% Dextrose infusion bag) | | SOLUTION 2 (1 Vial in 1000mL 5% Dextrose infusion bag) | |
| | | | | 0 Hour | 24 Hours | 0 Hour | 24 Hour |
| 1. | Description | Clear Colourless Solution, free from visible particles. | | Clear Colourless Solution, free from visible particles. | Clear Colourless Solution, free from visible particles. | Clear Colourless Solution, free from visible particles. | Clear Colourless Solution, free from visible particles. |
| 2. | pH | Between 3.5 and 6.0 | | 4.64 | 4.65 | 4.57 | 4.51 |
| 3. | Assay by HPLC | 90.0% to 110.0% | | 94.4% | 95.2% | 97.2% | 97.1% |
| 4. | Related substances by HPLC | d) Ferrocyanide | Not more than 0.04% | Not Detected | Not Detected | Not Detected | Not Detected |
| | | e) Any unspecified impurity | Not more than 0.2% | Not Detected | Not Detected | Not Detected | Not Detected |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | f) Total impurities | Not more than 1.0% | Not Detected | Not Detected | Not Detected | Not Detected |

DISCUSSION:

sodium nitroprusside injection 50 mg/2ml-2 ml vial,

batch no: E0010219 in solution 1 and solution 2 results of the data's were collected,

As its meets the acceptance criteria.

**RESULTS**

**SODIUM NITROPRUSSIDE INJECTION 50 mg/2mL-2 mL vial,**
**BATCH NO: E0010319 IN SOLUTION 1 AND SOLUTION 2**

**TABLE : 18**

| S.No. | Parameter | Acceptance criteria | | Results obtained | | | |
|---|---|---|---|---|---|---|---|
| | | | | SOLUTION 1 (1 Vial in 250 mL 5% Dextrose infusion bag) | | SOLUTION 2 (1 Vial in 1000mL 5% Dextrose infusion bag) | |
| | | | | 0 Hour | 24 Hours | 0 Hour | 24 Hour |
| 1. | Description | Clear Colourless Solution, free from visible particles. | | Clear Colourless Solution, free from visible particles. | Clear Colourless Solution, free from visible particles. | Clear Colourless Solution, free from visible particles. | Clear Colourless Solution, free from visible particles. |
| 2. | pH | Between 3.5 and 6.0 | | 4.64 | 4.61 | 4.49 | 4.50 |
| 3. | Assay by HPLC | 90.0% to 110.0% | | 97.8% | 97.9% | 100.9% | 100.8% |
| 4. | Related substances by HPLC | g) Ferrocyanide | Not more than 0.04% | Not Detected | Not Detected | Not Detected | Not Detected |
| | | h) Any unspecified impurity | Not more than 0.2% | Not Detected | Not Detected | Not Detected | Not Detected |
| | | i) Total impurities | Not more than 1.0% | Not Detected | Not Detected | Not Detected | Not Detected |

DISCUSSION:

sodium nitroprusside injection 50 mg/2ml-2 ml vial,
batch no: E0010319 in solution 1 and solution 2 results of the data's were collected,As its meets the acceptance criteria.

**RS- NITROPRESS (Sodium Nitroprusside Injection 50 mg/2mL), B.NO.690103F IN SOLUTION 1 ANDSOLUTION 2**

**TABLE : 19**

| S.No. | Parameter | Acceptance criteria | | Results obtained | | | |
|---|---|---|---|---|---|---|---|
| | | | | SOLUTION 1 (1 Vial in 250 mL 5% Dextrose infusion bag) | | SOLUTION 2 (1 Vial in 1000mL 5% Dextrose infusion bag) | |
| | | | | 0 Hour | 24 Hours | 0 Hour | 24 Hour |
| 1. | Description | Clear Colourless Solution, free from visible particles. | | Clear Colourless Solution, free from visible particles. | Clear Colourless Solution, free from visible particles. | Clear Colourless Solution, free from visible particles. | Clear Colourless Solution, free from visible particles. |
| 2. | pH | Between 3.5 and 6.0 | | 4.56 | 4.61 | 4.40 | 4.46 |
| 3. | Assay by HPLC | 90.0% to 110.0% | | 103.1% | 103.5% | 106.9% | 104.9% |
| 4. | Related substances by HPLC | j) Ferrocyanide | Not more than 0.04 % | Not Detected | Not Detected | Not Detected | Not Detected |
| | | k) Any unspecified impurity | Not more than 0.2% | Not Detected | Not Detected | Not Detected | Not Detected |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | l) Total impurities | Not more than 1.0% | Not Detected | Not Detected | Not Detected | Not Detected |

DISCUSSION: **RS- NITROPRESS (Sodium Nitroprusside Injection 50 mg/2mL), B.NO.690103F** in solution 1 and solution 2 results of the data's were collected,As its meets the acceptance criteria.

| S.No. | Parameter | Acceptance criteria | Results obtained | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | SOLUTION 1 | | | | | | | |
| | | | Generic product Exhibit batches | | | | | | RS- sample | |
| Batch Number | | | B.No: E0010119 | | B.No: E0010219 | | B.No: E0010319 | | 690103F (NITROPRESS) | |
| AR.Number | | | QC/ST/17/0777 | | QC/ST/17/0778 | | QC/ST/17/0779 | | QC/ST/17/0780 | |
| | | | 0 Hour | 24 Hours | 0 Hour | 24 Hours | 0 Hour | 24 Hours | 0 Hour | 24 Hours |
| 1. | Description | Clear Colourless Solution, free from visible particles. | Clear Colourless Solution, free from visible particles. | Clear Colourless Solution, free from visible particles. | Clear Colourless Solution, free from visible particles. | Clear Colourless Solution, free from visible particles. | Clear Colourless Solution, free from visible particles. | Clear Colourless Solution, free from visible particles. | Clear Colourless Solution, free from visible particles. | Clear Colourless Solution, free from visible particles. |
| 2. | pH | Between 3.5 and 6.0 | 4.68 | 4.57 | 4.64 | 4.65 | 4.64 | 4.61 | 4.56 | 4.61 |
| 3. | Assay by HPLC | 90.0% to 110.0% | 98.1% | 98.4% | 94.4% | 95.2% | 97.8% | 97.9% | 103.1% | 103.5% |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 4. | Related substances by HPLC | a) Ferrocyanide | Not more than 0.04 % | Not Detected | Not Detected | Not Detected | Not Detected | Not Detected | Not Detected | Not Detected | Not Detected |
| | | b) Any unspecified impurity | Not more than 0.2% | Not Detected | Not Detected | Not Detected | Not Detected | Not Detected | Not Detected | Not Detected | Not Detected |
| | | c) Total impurities | Not more than 1.0% | Not Detected | Not Detected | Not Detected | Not Detected | Not Detected | Not Detecte d | Not Detected | Not Detected |

**TABLE:20 COMPARISION OF ADMIXTURE STUDY RESULTS OF RS VS GENERIC DRUG PRODUCT EXHIBIT BATCHES IN SOLUTION 1(1 Vial in 250 mL 5% Dextrose infusion bag)**

**TABLE:21 COMPARISION OF ADMIXTURE STUDY RESULTS OF RS VS GENERIC DRUG PRODUCT EXHIBIT BATCHES IN SOLUTION 2(1 Vial in 250 mL 5% Dextrose infusion bag)**

| S.No. | Parameter | Acceptance criteria | Results obtained | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | SOLUTION 2 | | | | | | | |
| | | | Generic product Exhibit batches | | | | | | RS- sample | |
| Batch Number | | | B.No: E0010119 | | B.No: E0010219 | | B.No: E0010319 | | 690103F (NITROPRESS) | |
| AR.Number | | | QC/ST/17/0777 | | QC/ST/17/0778 | | QC/ST/17/0779 | | QC/ST/17/0780 | |
| | | | 0 Hour | 24 Hours | 0 Hour | 24 Hours | 0 Hour | 24 Hours | 0 Hour | 24 Hours |
| 1. | Description | Clear Colourless Solution, free from visible particles. | Clear Colourless Solution, free from visible particles. | Clear Colourless Solution, free from visible particles. | Clear Colourless Solution, free from visible particles. | Clear Colourless Solution, free from visible particles. | Clear Colourless Solution, free from visible particles. | Clear Colourless Solution, free from visible particles. | Clear Colourless Solution, free from visible particles. | Clear Colourless Solution, free from visible particles. |
| 2. | pH | Between 3.5 and 6.0 | 4.53 | 4.45 | 4.57 | 4.51 | 4.64 | 4.49 | 4.50 | 4.61 |
| 3. | Assay by HPLC | 90.0% to 110.0% | 99.0% | 100.3% | 97.2% | 97.1% | 100.9% | 100.8% | 106.9% | 104.9% |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 4. | Related substances by HPLC | d) Ferrocyanide | Not more than 0.04 % | Not Detected | Not Detected | Not Detected | Not Detected | Not Detected | Not Detected | Not Detected | Not Detected |
| | | e) Any unspecified impurity | Not more than 0.2% | Not Detected | Not Detected | Not Detected | Not Detected | Not Detected | Not Detected | Not Detected | Not Detected |
| | | f) Total impurities | Not more than 1.0% | Not Detected | Not Detected | Not Detected | Not Detected | Not Detected | Not Detecte d | Not Detected | Not Detected |

**ADDITIONAL INFORMATION:**

- Samples were loaded in long term storage condition 25°C±2°C/60%RH±5%RH and Admixture study analysis will be performed for 0, 24 and 36 hours at 24$^{th}$ month time point.

**SUMMARY:**

- Admixture study was performed by diluting exhibit batch samples of **Sodium Nitroprusside Injection 50 mg/2mL-2mL** and RS NITROPRESS samples with 5% w/v Dextrose injection diluents present in 250 mL and 1000 mL infusion bags, accordingly physical and chemical test parameters were evaluated.

- Initial time point Admixed samples in 5% w/v Dextrose injection 250 mL and 1000 mL infusion bag, are analysed at 0 hrs and 24 hrs after dilution for the test parameter Description, pH, Assay and Related Substances and the results are found within the acceptance criteria of specification.

## CONCLUSION:

- Based on the obtained results, it is confirmed that the admixed generic product is stable for 24 hours, after admixing with 5% Dextrose injection in 250 mL infusion bag and 1000 mL infusion bag.
- The results obtained for admixture study of RS - NITROPRESS injection batch Number: 690103F were compared with the results as obtained for admixture study of generic product batche for Sodium Nitroprusside Injection 50 mg/2mL-2mL, Batch and were found to be comparable.

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