Panacea Journal of Pharmacy and Pharmaceutical Sciences 2016:5(2);51-63

International Journal

PJPPS

Panacea Research Library

http://internationaljournal.org.in/journal/index.php/pjpps

Panacea Journal of Pharmacy and Pharmaceutical Sciences

ISSN: 2349 7025

Original Research Article **Volume 5 Issue 2**

FORMULATION AND CHARACTERIZATION OF PARENTRAL DOSAGE FORM FOR POORLY SOLUBLE DRUGS

Pushpendra Mishra*, Harish Kumar, Mukesh Patel, Dr DP Chatterjee

Mittal Institute of Pharmacy, Bhopal, Madhya Pradesh, India

Article history:

Received: 14th June 2016

Received in revised form: 18th June 2016

Accepted: 25th June 2016

Available online: 30th June 2016

Corresponding author:

Pushpendra Mishra*

E-mail:

pushpendra.mishra1990@gmail.com

***Present address*:**

Mittal Institute of Pharmacy, Bhopal, Madhya Pradesh, India

These authors have no conflict of interest to declare.

Abstract

The parenteral administration route is the most common and efficient for delivery of active drug substances with poor bio-availability and the drugs with a narrow therapeutic index. But parenteral route offers rapid onset of action with rapid declines of systemic drug Level. For the sake of effective treatment it is often desirable to maintain systemic drug levels within the therapeutically effective concentration range for as long as treatment calls for. It requires frequent injection, which ultimately leads to patient discomfort. For this Reason, drug delivery system which can reduce total number of injection throughout the effective treatment, improve patient compliance as well as Pharmacoeconomic. These biodegradable Injectable drug delivery system offer attractive opportunities for protein delivery and could possibly extend patent life of protein drugs. This article explores various prolonged release parenteral drug delivery system and their strategies of preparation, their potential benefits/drawbacks and in-vitro testing methods.

Keywords: Missing ??

INTRODUCTION

Parenteral administration of drugs involves the injection of therapeutic agents, in the form of solutions, suspensions or emulsions, into the body. In so doing, one of the major barriers to drug entry (the skin) is breeched[1]. Parenteral formulations have been officially recognized since the mid 19th century when morphine solution appeared in the 1874 addendum to the British Pharmacopoeia (1867). Currently many classes of drug are formulated as parenteral dosage forms and, indeed, the control of certain disease states is dependent on parenteral administration, e.g. type 1 diabetes mellitus. Parenteral products are therefore essential components of modern medicine.

There are various means by which drugs are delivered to the body for therapy such as tablets, capsules etc. Disadvantages of this kind of therapy are peak and trough profile leading to greater chances of adverse effects. Therapy is inefficient since large amount of drug is lost in the vicinity of the target organ. Parenterals are administered by injection under or through one or more layers of skin or mucous membrane into body tissues and many times directly into blood overcome these problems.

Parenteral dosage forms and delivery systems include injectables (ie, solutions, suspensions, emulsions, and dry powders for reconstitution), intramammary infusions, intravaginal delivery systems, and implants.

- **Solution for injection** is a mixture of 2 or more components that form a single phase that is homogeneous down to the molecular level. “Water for injection” is the most widely used solvent for parenteral formulations. However, a nonaqueous solvent or a mixed aqueous/nonaqueous solvent system may be necessary to stabilize drugs that are readily hydrolyzed by water or to improve solubility. A range of excipients may be included in parenteral solutions, including antioxidants, antimicrobial agents, buffers, chelating agents, inert gases, and substances for adjusting tonicity. Antioxidants maintain product stability by being preferentially oxidized over the shelf life of the product. Antimicrobial preservatives inhibit the growth of any microbes that are accidentally introduced while doses are being withdrawn from multiple-dose bottles and act as adjuncts in aseptic processing of products. Buffers are necessary to maintain both solubility of the active ingredient and stability of the product. Chelating agents are added to complex and thereby inactivate metals, including copper, iron, and zinc, which generally catalyze oxidative degradation of drugs. Inert gases are used to displace the air in solutions and enhance product integrity of oxygen-sensitive drugs. Isotonicity of the formulation is achieved by including a tonicity-adjusting agent.

Failing to adjust the tonicity of the solution can result in the hemolysis or crenation of erythrocytes when hypotonic or hypertonic solutions, respectively, are given intravenously in quantities >100 mL. Injectable formulations must be sterile and free of pyrogens. Pyrogenic substances are primarily lipid polysaccharides derived from microorganisms, with those produced by gram-negative bacilli generally being most potent. Injectable solutions are very commonly used, and aqueous solutions given intramuscularly result in immediate drug absorption, provided precipitation at the injection site does not occur.

- **Dry powder** for parenteral administration is reconstituted as a solution or as a suspension immediately prior to injection. The principal advantage of this dosage form is that it overcomes the problem of instability in solution.
- **Emulsion** for injection is a heterogeneous dispersion of one immiscible liquid in another; it relies on an emulsifying agent for stability. Parenteral emulsions are rare because it is seldom necessary to achieve an emulsion for drug administration. Untoward physiologic effects following intravenous administration may occur, including emboli in blood vessels if the droplets are >1 μm in diameter. Formulation options for injectable emulsions are also severely restricted because suitable stabilizers and emulsifiers are very limited. Examples of parenteral emulsions include oil-in-water sustained-release depot preparations, which are given intramuscularly, and water-in-oil emulsions of allergenic extracts, which are given subcutaneously.
- **Suspension** for injection consists of insoluble solid particles dispersed in a liquid medium, with the solid particles accounting for 0.5-30% of the suspension. The vehicle may be aqueous, oil, or both. Caking of injectable suspensions is minimized through the production of flocculated systems, comprising clusters of particles (flocs) held together in a loose open structure. Excipients in injectable suspensions include antimicrobial preservatives, surfactants, dispersing or suspending agents, and buffers. Surfactants wet the suspended powders and provide acceptable syringeability while suspending agents modify the viscosity of the formulation. The ease of injection and the availability of the drug in depot therapy are affected by the viscosity of the suspension and the particle size of the suspended drug. These systems afford enhanced stability to active ingredients that are prone to hydrolysis in aqueous solutions. Injectable suspensions are commonly used. Compared with that of injectable solutions, the rate of drug absorption of injectable suspensions is prolonged because additional time is required for disintegration and dissolution of the suspended drug particles. The slower release of drug from an oily suspension compared with that of an aqueous suspension is attributed to the additional time taken by drug

particles suspended in an oil depot to reach the oil/water boundary and become wetted before dissolving in tissue fluids.

DRUG CHARACTERIZATION

LAMOTRIGINE

MELTING POINT DETERMINATION

Melting point of lamotrigine was determined by open capillary method. Drug sample was filled in a capillary which was previously sealed at one end. The capillary was then placed into Thiel's tube, filled with liquid paraffin, along with a thermometer. The tube was heated and melting point was recorded.

Results and conclusion

Melting point of lamotrigine was found to be 216-220ºC which is same as reported in literature.

UV SPECTROPHOTOMETRIC ANALYSIS OF DRUG SAMPLE

UV spectrum of lamotrigine in demineralized water

Fifty mg of lamotrigine was accurately weighed and transferred to 100 ml volumetric flask. The drug was dissolved by addition of 50 ml methanol and volume was made upto 100 ml with methanol so as to obtain solution of 500 µg/ml. Then 10 ml of this solution was taken in another 100 ml volumetric flask, and volume was made upto 100 ml with demineralised water. The concentration of this resulting solution (stock solution) was 50 µg/ml. Then 4 ml aliquot of the stock solution was taken in 10 ml volumetric flask and volume was made up with demineralized water to obtain the solution of 20 µg/ml. The sample was scanned between 200 nm to 400 nm on a double beam UV/Visible spectrophotometer (Shimadzu® 160-A). The UV spectrum so obtained of lamotrigine is shown in fig. 5.1

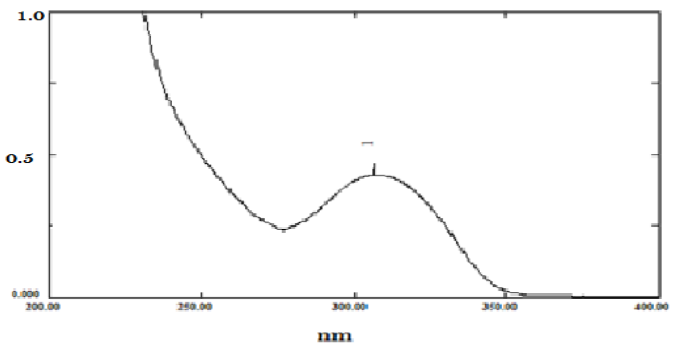

Fig. 5.1: UV spectrum of lamotrigine in demineralized water

Results and conclusion

The UV spectrum of lamotrigine showed peak at 306 nm which is same as reported in literature.

UV spectrum of lamotrigine in 0.1 N Hydrochloric Acid (pH 1.2)

Fifty mg of lamotrigine was accurately weighed and transferred to 100 ml volumetric flask. The drug was dissolved by addition of 50 ml methanol and volume was made upto 100 ml with methanol so as to obtain solution of 500 µg/ml. Then 10 ml of this solution was taken in another 100 ml volumetric flask, and volume was made upto 100 ml with 0.1N hydrochloric acid. The concentration of this resulting solution (stock solution) was 50 µg/ml. Then 4 ml aliquot of the stock solution was taken in 10 ml volumetric flask and volume was made up with 0.1N hydrochloric acid to obtain the solution of 20 µg/ml. The sample was scanned between 200 nm to 400 nm on a double beam UV/Visible spectrophotometer (Shimadzu® 160-A). The UV spectrum so obtained of lamotrigine is shown in fig. 5.2

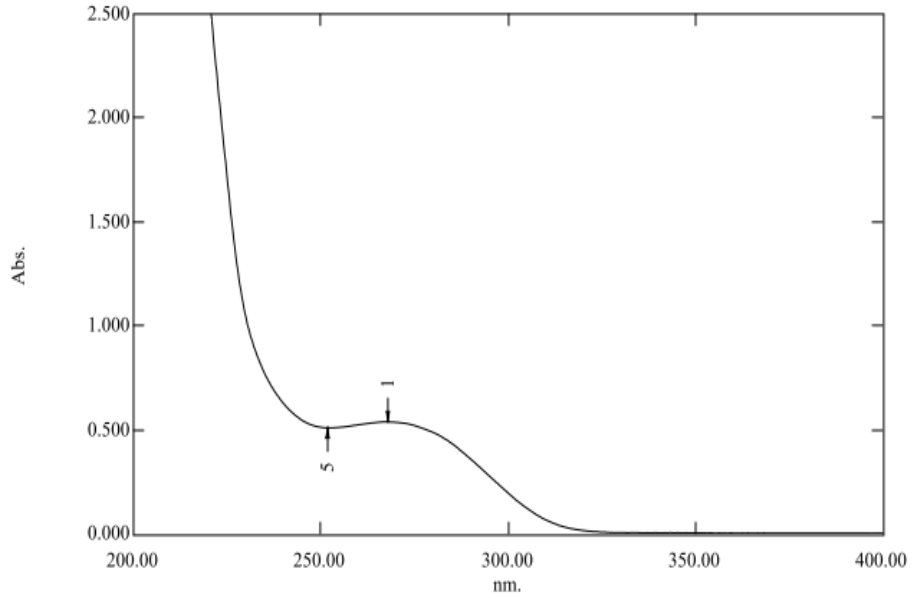

Fig. UV spectra of lamotrigine in 0.1 N hydrochloric acid (pH 1.2)

Results and conclusion

The UV spectrum of lamotrigine in 0.1 N hydrochloric acid showed peak at 267 nm which is same as reported in literature.

RIFAMPICIN

MELTING POINT DETERMINATION

Melting point of rifampicin was determined by open capillary method. Drug sample was filled in a capillary which was previously sealed at one end. The capillary was then placed into Thiel's tube, filled with liquid paraffin, along with a thermometer. The tube was heated and melting point was recorded.

Results and conclusion

Melting point of rifampicin was found to be 182-186ºC which is same as reported in literature.

UV SPECTROPHOTOMETRIC ANALYSIS OF DRUG SAMPLE

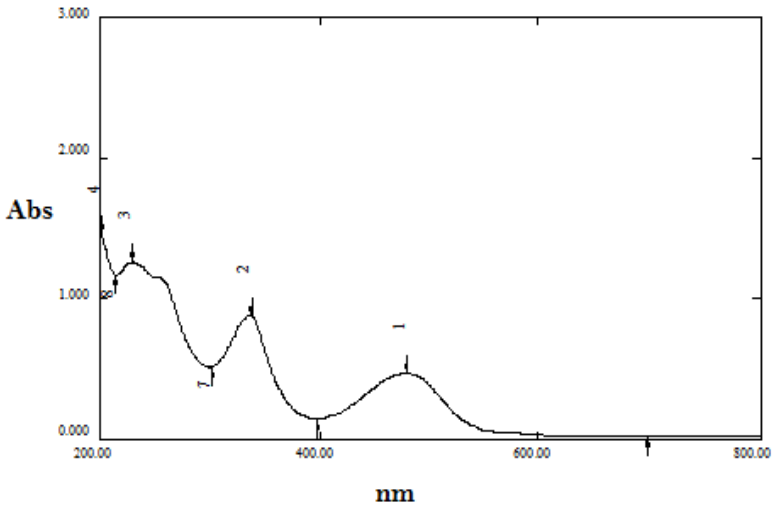

Figure: Spectra of rifampicin in ethanol---30 mcg/ml

PREFORMULATION STUDIES OF LAMOTRIGINE

PREPARATION OF CALIBRATION CURVES

The standard calibration curves of lamotrigine were prepared in demineralised water and demineralised water containing different solubilizers using double beam UV/Visible spectrophotometer (Shimadzu 1700). The data obtained were then subjected to linear regression analysis.

CALIBRATION CURVE OF LAMOTRIGINE IN DEMINERALIZED WATER

Fifty milligram of lamotrigine was accurately weighed and transferred to 100 ml volumetric flask. The drug was dissolved by addition of 50 ml methanol and volume was made upto 100 ml with methanol so as to obtain solution of 500 µg/ml. Then 10 ml of this solution was taken in another 100 ml volumetric flask, and volume was made upto 100 ml with demineralised water. The concentration of this resulting solution (stock solution) was 50 µg/ml. Appropriate dilutions from the stock solution were made with demineralised water in the concentration range of 10 µg/ml to 50 µg/ml. The absorbances of these solutions were measured on double beam UV/Visible spectrophotometer (Shimadzu 1700) at 306 nm. The absorbances data obtained from various concentrations were subjected to linear regression analysis. The observations are recorded in the table 6.1 and graphically represented in fig. 6.1

Table Absorbance data for calibration curve of lamotrigine in demineralised water at 306 nm

S. No.	Concentration (µg/ml)	Absorbance
1	0	0
2	10	0.241
3	20	0.483
4	30	0.727
5	40	0.981
6	50	1.271

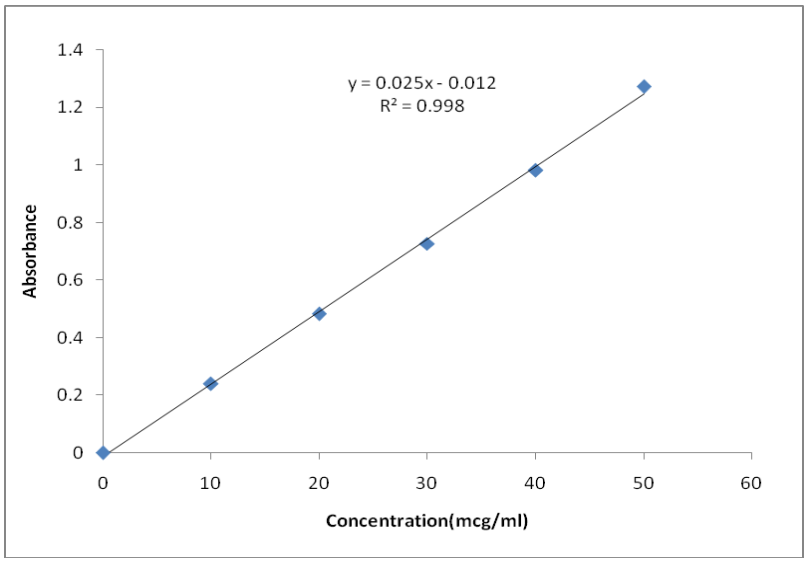

Figure: Calibration curve of lamotrigine in demineralized water at 306 nm

CALIBRATION CURVE OF LAMOTRIGINE IN PRESENCE OF SOLUBILIZERS

Fifty milligrams of lamotrigine drug was accurately weighed and transferred to a 100 ml volumetric flask. Sufficient volume of 25% aqueous solution of solubilizer was added to it for complete dissolution of drug. After complete dissolution of drug, sufficient demineralized water was added to make up the volume up to the mark. The flask was shaken to produce a homegenous stock solution. This stock solution was further diluted with demineralized water to get various standard solutions containing 10, 20, 30, 40 and 50 µg/ml of drug. The absorbances of these solutions were measured on UV/Visible spectrophotometer (Shimadzu 1700) at 306 nm against respective reagent blanks. The absorbance data obtained from various concentrations were subjected to linear regression analysis. The data were recorded in table 6.2 to 6.4 and graphically represented in fig. 6.2 to fig. 6.4.

Table: Absorbance data for calibration curve of lamotrigine in demineralized water containing 25% PEG 4000 at 306 nm

S. No.	Concentration (µg/ml)	Absorbance
1	0	0
2	10	0.239
3	20	0.480
4	30	0.725
5	40	0.978
6	50	1.267

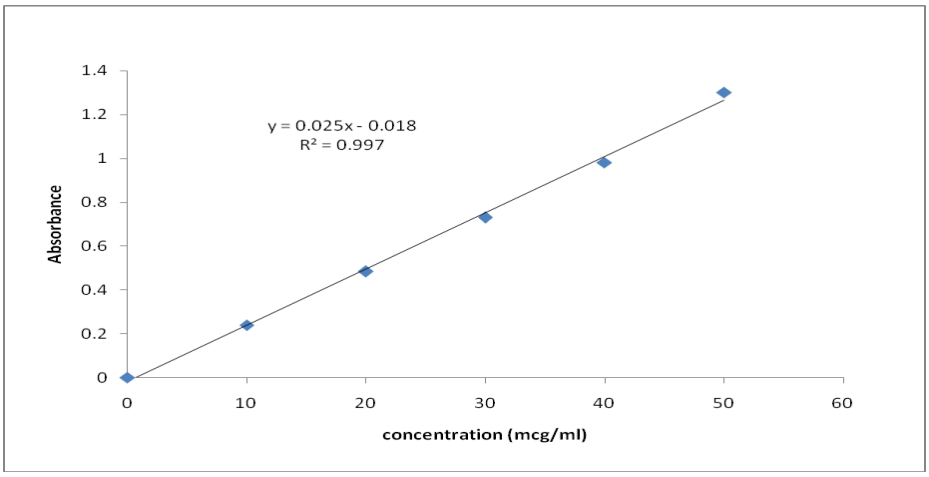

Fig. Calibration curve of lamotrigine in demineralised water containing 25% PEG 4000 at 306 nm

PREFORMULATION STUDIES OF RIFAMPICIN

PREPARATION OF CALIBRATION CURVE IN ETHANOL

Fifty mg of rifampicin was accurately weighed and transferred to 100 ml volumetric flask. The drug was dissolved by addition of 60 ml ethanol and volume was made upto 100 ml with ethanol so as to obtain solution of 500 µg/ml. Appropriate dilutions from the stock solution were made with ethanol in the concentration range of 10 µg/ml to 50 µg/ml. The absorbances of these solutions were measured on double beam UV/Visible spectrophotometer (Shimadzu 1700) at 475 nm. The absorbances data obtained from various concentrations were subjected to linear regression analysis. The observations are recorded in the table 7.1 and graphically represented in fig. 7.1

Table Absorbances for calibration curve of rifampicin in ethanol at 475 nm

S. No.	Concentration (µg/ml)	Absorbance
1	0	0
2	10	0.172
3	20	0.348
4	30	0.512
5	40	0.712
6	50	0.877

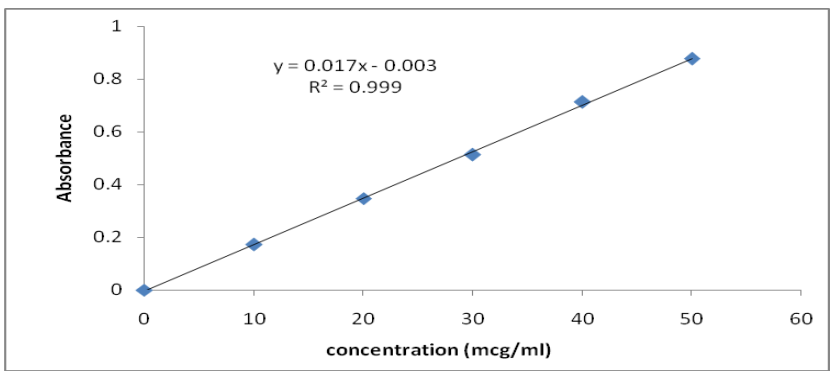

Fig. Calibration curve of rifampicin in ethanol at 475 nm

INTERFERENCE STUDY OF SOLUBILIZERS IN UV SPECTROPHOTOMETRIC ESTIMATION OF DRUG

The solutions of each solubilizing agents of known concentration 1000 µg/ml in ethanol were prepared and scanned on UV/Visible spectrophotometer (Shimadzu 1700) against same reagent solution in the region from 200-800 nm. The cut off wavelength (nm) and corresponding absorbances so obtained were recorded in table 7.2.

Table UV spectral analysis data of solubilizers for cut-off wavelength

S. No.	Solubilizer	Cut-off wavelength (nm)	Absorbance
1.	Thymol	305.0	0.012
2.	Menthol	298.5	0.008
3.	Camphor	298.5	0.007
4.	Phenol	326.0	0.016
5.	Benzyl alcohol	297.0	0.009
6.	Oleic acid	328.5	0.003
7.	Ethyl oleate	423.5	0.011

Result and discussion: It is evident from the table 7.2 that all of the used solubilizers absorbs below 475 nm, so they will not interfere in the UV estimation of rifampicin at 475 nm.

DEVELOPMENT OF AQUEOUS PARENTERAL FORMULATION

The present investigation was proposed to solubilise lamotrigine using combination of various physiologically compatible solubilizers. By increasing the solubility of drug, it might be possible to formulate the small volume parenteral, which will be useful in patient with status epilepticus in which parenteral administration of lamotrigine may be required to achieve the required therapeutic plasma concentration rapidly.

OPTIMIZATION OF VARIOUS PARAMETERS FOR AQUEOUS INJECTION FORMULATION OF LAMOTRIGINE

Selection of solubilizer blend for injection formulation

On the basis of results obtained from solubility studies, mixed blend B-19, B-21, B-22 and B-23 were selected. To develop 3 ml of lamotrigine injection, the amount of solubilizers that will be administered through each mixed blend was determined. Injection formulations of various strengths were developed based on solubility of lamotrigine in individual blends. The proposed formulations are shown in table 8.1 to 8.4.

Table Formulation: B-19

S. No.	Ingradients	Prescribed formula	Working formula
1	Lamotrigine	4.5 mg	60 mg
2	Lignocaine hydrochloride	0.15 gm	2 gm
3	Niacinamide	0.15 gm	2 gm
4	PEG 400	0.15 ml	2 ml
5	PEG 4000	0.12 gm	1.6 gm
6	Ethanol	0.09 ml	1.2 ml
7	PVP 40000	0.09 gm	1.2 gm
8	Sterile water for injection	q. s. to 3 ml	q. s. to 40 ml

DEVELOPMENT OF OILY INJECTION FORMULATION OF RIFAMPICIN

The present investigation was proposed to solubilise rifampicin in castor oil using combination of various solubilizers. By increasing the solubility of drug in oil, it might be possible to formulate the small volume depot injection, which will be useful for prolonged release of drug. Depot provides advantage over orally administered preparations that a single injection will be sufficient for one or more weeks, whereas tablets, for example, must generally be ingested daily.

OPTIMIZATION OF VARIOUS PARAMETERS FOR OILY INJECTION FORMULATION OF RIFAMPICIN

Selection of solubilizer blend for injection formulation

On the basis of results obtained from solubility studies, mixed blend OB-6, OB-10, OB-11, OB-12, OB-16, OB-20 and OB-22 were selected. To develop 2.5 ml of rifampicin oily injection, the amount of solubilizers that will be administered through each mixed blend was determined. Injection formulations of various strengths were developed based on solubility of rifampicin in individual blends. The proposed formulations are shown in table 9.1 to 9.7.

Table 9.1: Formulation OB-6

S. No.	Ingredients	Prescribed formula (31.75 mg/2.5 ml)	Working formula (50 ml batch)
1	Rifampicin	31.75 mg	635 mg
2	Menthol	0.125 mg	2.5 gm
3	Camphor	0.125 mg	2.5 gm
4	Phenol	0.125 mg	2.5 gm
5	Benzyl alcohol	0.125 ml	2.5 gm
6	Castor oil	q. s. to 2.5 ml	q. s. to 50 ml

REFERENCE:

1. http://www.merckvetmanual.com/mvm/index.jsp?cfile=htm/bc/190120 (Accessed February, 2010)
2. David, J., *Fasttrack: Pharmaceutics dosage form and design*. 1st ed.; Pharmaceutical press: London, 2008: p 103-112.
3. http://www.google.co.in/imgres?q=routes+of+parenteral+administration
4. Deluca, P.P., Boylan, J.C., 2005. Formulation of small volume parenterals, In: Kenneth, E.A., Herbert, A.L., Lachman, L., (Ed.), Parenteral Dosage Forms: Parenteral Medications, 2nd ed., Marcel Dekker Inc., New York, 1, pp. 238-240.
5. Ansel, H.C., Allen, L.V., Popovich, N.G., 2002. Pharmaceutical dosage forms and drug delivery systems, 7th ed., Lippincott Williams and Wilkins, Philadelphia, pp. 408.
6. Jindal, K.C., Boldhane, S.P., 2006. Parenteral products, In: Jain, N.K., (Ed.), Pharmaceutical Product Development, CBS Publishers and Distributers, New Delhi, pp. 177.
7. Deluca, P.P., Boylan, J.C., 2005. Formulation of small volume parenterals, In: Kenneth, E.A., Herbert, A.L., Lachman, L., (Ed.), Parenteral Dosage Forms: Parenteral Medications, 2nd ed., Marcel Dekker Inc., New York, 1, pp. 172.
8. Chien, Y.W., Cabana, B.E., Mares, S.E., Novel Drug Delivery Systems: Fundamentals, Developmental Concepts and Biomedical Assessments, 1st ed., Marcel Dekker Inc., New York and Basel, 3(1982) 219-224.
9. Robinson, J.R., Lee, V.H.L., Controlled Drug Delivery: Fundamentals and Applications, 2nd ed., Marcel Dekker Inc., New York and Basel, Part- I, 433-454.
10. Banker, G.S., Rhodes, C.T., Modern Pharmaceutics, 4th ed., Marcel Dekker Inc., New York and Basel, (2007) 382-385.
11. Wise, D.L., Handbook of Pharmaceutical Controlled Release Technology, 1st ed., Marcel Dekker Inc., New York and Basel, (2005) 329-338.