International Journal of Pharmacy and Industrial Research (IJPIR)
IJPIR |Vol.14 | Issue 4 | Oct - Dec -2024
www.ijpir.com
DOI : https://doi.org/10.61096/ijpir.v14.iss4.2024.416-427
ISSN: 2231-3656
Print: 2231-3648

Research

Formulation and development of nanosuspension ofbromhexine hydrochloride

S. Kavibharathi, Ashik P M, Dr. S. Chandra, Dr. N. Senthil Kumar

Department Of Pharmaceutics, J.K.K. Munirajah Medical Research FoundationCollege Of Pharmacy, Komarapalayam-638183. The Tamilnadu Dr. Mgr. Medical University, Chennai

***Author for Correspondence: S. Kavibharathi**
Email: jaasamri5@gmail.com

Published on: 15 Nov 2024

Published by:
DrSriram Publications

Abstract

The aim of the present investigation was to develop, formulate and evaluation ofbromhexine hydrochloride nanosuspension for treatment of bronchial asthma. Bromhexinehydrochloride is a mucolytic agent used to treat respiratory diseases associated with viscid or excessive mucus accumulated in respiratory tract. The present research involved to find out the effect of differ• ent polymer and their ratio on the formulation of Bromhexine hydrochloride oral nanosuspension. The prepared nanosuspension were evaluated for particle size, zeta potential, SEM analysis, Saturation solubility, drug content, viscosity and In-vitro drug release studies. Saturation solubility studies and In-vitro drug release studies shows that the prepared nanosuspension has increased solubility and diffusion rate compared to pure drug. Among all the formulations, F3 has shown the better results like average particle size of 278-450 nm, zeta poten• tial was found to be 27.3 mv and the drug release was 94.55% for bromhexine hydrochloride at the 12th hour.

Keywords: Bromhexine hydrochloride, nanosuspension, High speed homoge• nization, in-vitro studies.

INTRODUCTION

Nano Drug Delivery System
Nanotechnology

It is a technological development on the nanometer scale, usually 0.1 to 100 nm. Nanotechnology (the science of the small) deals with the study of molecular and atomic particles. This technology can be used to solve the problems associated with these conventional approaches for solubility and bioavailability enhancement

Nanosuspension

Nanosuspensions are colloidal dispersions of nano-sized drug particles stabilized by surfactants. It is a biphasic system compromising of pure drug particles dispersed in an aqueous vehicle in which the diameter of the suspended particle is less than 1µm in size. The solubility of a drug is a major challenge for the development of formulation. A poorly water-soluble drug exhibit inadequate and variable bioavailability and finally leads to

gastrointestinal toxicity due to slow drug absorption, when administered orally. For such drugs, solubility is the most important parameter, to achieve their desired concentration insystemic circulation for therapeutic effect. The drug belonging to Biopharmaceutics classification system (BCS) classes, II and Iv have these problems. The rate-limiting step for BCS class II drugs is the solubility and drug release from the dosage form; so increasing the solubility of BCS class II drugs, in turn, increases the bioavailability.

The formulation of nano-sized particles can be implemented to all drug compounds belonging to biopharmaceutical classification system (BCS) classes II and IV to increase their solubility and hence partition into gastrointestinal barrier. Micronization is used for class II drugs of (BCS), i.e. drugs having a good permeability and poor solubility. There are many conventional methods for increasing the solubility of poorly soluble drugs, which include micronization, solubilization using co-solvents, salt form, surfactant dispersions, precipitation technique, and oily solution.

The use of nanotechnology to formulate poorly water soluble drugs as nanosuspension offers the opportunity to address nature of the deficiency associated with this class of drugs. Nanosuspension has been reported to enhance absorption and bioavailability it may help to reduce the dose of the conventional oral dosage forms therefore to maintain the therapeutics concentration it may be used as nanosuspension with a nanoparticle size in the nano range typically between 1-1000nm is proposed. The present study is to designed bromhexine hydrochloride nanosuspension (BHS) as a novel controlled dosage form that could release the drug in a controlled fashion at the site to have better therapeutic efficiency at a much lower dose .Drug particle size reduction leads to an increase in surface area and consequently in the rate of dissolution as described bythe Nernst–Brunner and Levich modification of the Noyes–Whitney equation .In addition, an increase in saturation solubility is postulated by particle size reduction due to anincreased dissolution pressure explained by the Ostwald–Freundlich equation. Depending on the production technique applied changes in crystalline structure of drug particles may also occur. An increasing amount of amorphous drug fraction could induce higher saturation solubility.

Nanosuspensions have some following advantages: firstly, drugs no longer need to be in the soluble form. It is effective for those molecules insoluble in oils; secondly, the high drug loading can be achieved as a drug exists in the form of pure solids, and can significantly reduce the administration volume of high dose; thirdly, nanosuspensions can increase the physical and chemical stability of drugs as they are actually in the solid state; finally, nanosuspension can provide the passive targeting.

Characterization Of Nanosuspension

Nanosuspensions are evaluated as conventional suspensions like appearance, color,odour, assay, related impurities etc. Along with that particle size, zeta potential, morphology, dissolution study, in-vivo studies, polydispersity index (PDI), scanning electron microscopy (SEM) transmission electron microscopy (TEM).

Aim And Objectives

The aim of the present study is to formulation and development of nanosuspensionof Bromhexine Hydrochloride.

The purpose of this investigation was to increase the stability and dissolution rateby the preparation of nanosuspension. Enhancing the solubility of the drug. Enhancing the bioavailability of Bromhexine hydrochloride. To improve patient compliance. Authentication of drug sample:

MATERIALS AND METHODS

Materials, Chemicals, and Reagents

Table 1: List of Chemicals and Reagents

Sl. No	Materials	gifted from
1	Bromhexine Hydrochloride	Swapnroop Drugs & Pharmaceuticals, Mumbai
2	HPMC K15M	Fisher Scientific, Mumbai
3	Eudragit RS100	Fisher Scientific, Mumbai
4	Lecithin	Fisher Scientific, Mumbai
5	Tween-80	Karnataka Fine Chem., Bengaluru
6	Ethanol	Karnataka Fine Chem., Bengaluru

S/N	MATERIALS	USE	SOURCE
1	Bromhexine Hydrochloride	API	Swapnroop Drugs & Pharmaceuticals,Mumbai
2	Eudragit	Polymer	Fisher Scientific, Mumbai
3	HPMC K15M	Polymer	Fisher Scientific, Mumbai
4	Tween-80	Surfactent	Karnataka Fine Chem., Bengaluru
5	Lecithin	Stabilizer	Karnataka Fine Chem., Bengaluru
6	Ethanol	Solvent	Karnataka Fine Chem., Bengaluru
7	Silica Gel	TLC	Karnataka Fine Chem., Bengaluru
8	Hydrochloric Acid	Solvent	Karnataka Fine Chem., Bengaluru
9	Potassium Bromide	FTIR	Karnataka Fine Chem., Bengaluru

Instruments

Table 2: List of Instruments

S/N	INSTRUMENTS	MANUFACTURER
1	Electronic Balance	Citizen scales Pvt. Ltd, Mumbai
2	FT-IR	IR-Affinity-1-FTIR Spectrophotometer, Shimadzu, Japan
3	UV-Visible Spectrophotometer	UV-1800 Shimadzu UV Spectrophotometer, Shimadzu Corporation, Japan
4	Magnetic Stirrer	Remi Elektrotechnik Ltd., Vasai
5	High-pressure homogenization:	Elektrocraft [india] pvt. ltd.
6	Centrifuge	Remi Elektrotechnik Ltd., Vasai
7	Mechanical Stirrer	Remi Elektrotechnik Ltd., Vasai
8	Pen type pH meter	Equinox Electronics Ltd, Bengaluru
9	Sieve Shaker	Remi Elektrotechnik Ltd., Vasai
10	Dissolution apparatus	Veego Instrument Corporation, Mumbai
11	Stability Test Chamber	Servewell Instruments Pvt. Ltd., Bengaluru
12	Differential Scanning Calorimetry	Mettler Toledo DSC 822e
13	Powder X-Ray Diffraction	Shimadzu XRD-7000

METHODOLOGY

Preformulation test

Solubility of Bromhexine Hydrochloride

The solubility of Bromhexine Hydrochloride was performed in various solvents like water, ethanol, and methanol. Accurately one mg of drug was transferred in a clean and dry test tube and dissolved in 5ml of the solvents individually and shaken vigorously and the solubility of the drug was checked visually.

Melting point determination of Bromhexine Hydrochloride

The melting point of Bromhexine Hydrochloride was determined by using Thiele'stube method by taking a small amount of drug in a capillary tube closed at one end and placed in Thiele tube containing liquid petroleum and temperature at which drug melts was recorded. This was performed in triplicates and the average value was reported.

Retardation Factor of Bromhexine Hydrochloride by Thin Layer Chromatography

The Solvent System was prepared using Methanol: Chloroform: Triethanolaminein the ratio (5.5:4.5:0.5). A slurry of silica gel was prepared in a beaker by adding quantity sufficient of distilled water. Meanwhile, the solvent system is put in a beaker and closed with a Petri dish to allow its saturation. A slurry of silica gel is then kept in the beaker. The glass slide was clean and wiped with a clean cloth till it dried. The glass slides are then dipped in the slurry of silica gel (Dipping method). This was allowed uniform distribution of the stationary phase. Then air-dried and put in the oven at a temperature and time of 120ºC for 1 hour. This for activation, remove moisture and make theseparation to be clear. Sample put at a distance of 2cm from the bottom of the baseline by using a capillary tube. This slide keeps into the saturated mobile phase beaker. Glassslide removed when the mobile phase has reached 75% of the distance.

Ultraviolet Spectrum

Bromhexine Hydrochloride solution was prepared in methanol and diluted suitably.The UV spectrum of the solution was taken on UV Shimadzu 1800 UV/Vis double beam Spectrophotometer. The value was compared with the standard value.

Infrared Spectral studies

Method

Approximately 1 mg of the Bromhexine Hydrochloride was allowed to mix with about 100 mg of KBr (which is transparent to IR) in the ratio of 1:100. Thoroughly mixin a mortar. The mixture was pressed into a pellet die manually. Place it in Fourier Transform Infrared (FTIR) Spectrophotometer (Shimadzu corporation 8400S, Japan).

Differential Scanning Calorimetry (DSC)

DSC analysis of the drug was carried out by using Mettler Toledo DSC 822e73. The sample was heated at a heating rate of 100 C/min over the temperature range of30.0- 220.00 C.

Powder X-Ray Diffraction (PXRD)

Powder X-Ray Diffractometer analysis of the drug was carried out by using Shimadzu XRD-7000. These X-rays are directed at the sample, and the diffracted raysare collected. A key component of all diffraction is the angle between the incident and diffracted rays.

FTIR spectrophotometer

The compatibility of drug and polymer was analyzed using FTIR spectrophotometer. In this technique, 1mg of the sample and 100mg of potassium bromide (KBr) (1:100 ratio) was finely ground using mortar and pestle. A few mixtures were placed for 2 minutes under a hydraulic press compressed at 7kg/cm2 to form a transparent pellet. The pellet was kept in the sample holder and scanned from 4000 cm-1 to 400 cm-1 in Shimadzu FT-IR spectrophotometer. Samples were prepared for the drug (Bromhexine Hydrochloride), polymer (HPMC K15M) and physical mixture of drug and polymers. The spectra obtained were compared and interpreted for the functional group peaks.

Differential Scanning Calorimetry (DSC)

DSC analysis of the samples was carried out by using Mettler Toledo DSC 822e. Samples were heated at a heating rate of 100 C/min over the temperature range of 30.0- 220.00C. Accurately weighed samples (5–8 mg) were placed in non-hermetically sealed aluminum pans. An empty aluminum pan served as a reference. Samples were heated ona Pyris 1 DSC (Perkin-Elmer, USA) equipped with an Intra cooler 2P cooling accessory. The heating rate was 10 K/min and nitrogen purge 20 ml/min.

Fig 1: Preparation of nanosuspension

Formulation of Bromhexine Hydrochloride nanosuspension

Table 3: Formulation of Bromhexine Hydrochloride nanosuspension (F1-F8)

Ingredients/mg	F1	F2	F3	F4	F5	F6	F7	F8
Bromhexine Hydrochloride (mg)	24	24	24	24	24	24	24	24
HPMC E15(mg)	120	120	120	120	-	-	-	-
Eudragit RS100 (mg)	-	-	-	-	120	120	120	120
Lecithin (mg)	0.5	1	1.5	2	0.5	1	1.5	2
Tween80 (ml)	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8
Ethanol (ml)	10	10	10	10	10	10	10	10
Water (ml)	10	10	10	10	10	10	10	10

Evaluation of the Bromhexine Hydrochloride nanosuspension

The physicochemical evaluation studies were performed by using the parameters such as estimation of saturation solubility studies, %Drug content, drug entrapmentefficiency, viscosity measurements, zeta potential measurement, scanning electron microscopy, in vitro drug release and kinetic model studies.

Saturation solubility

Nanosuspension will increase the solubility and dissolution velocity. It can be helpful for the in vitro behavior of the formulation. When the particle size reduced to the nanometric range, dissolution velocity and dissolution pressure will be increase. This leads to the solubility due to the change in the surface tension.

Determination of drug content and entrapment efficiency

10ml of each formulation was taken and dissolved in isotonic solution and kept overnight. 10mg of nanosuspension was took and dilution was made up to 10µg/ml. The dilutions were filtered and analyzed using UV of their content uniformity. The absorbance of the formulation was using one cell in an UV-visible spectrophotometer. The instrument set the wavelength according to the drug. The drug content in each formulation was calculated based on the absorbance values of known standard solutions. The entrapmnent efficiency study was carried out by using 10 ml of the nanosuspension and centrifuge at 3500rpm for 30 mints. Supernated layer removed and unincorporated drug was measured by uv spectrophotometer.

Viscosity measurements

Viscosity of bromhexine hydrochloride nanosuspensions was measured by Brook field viscometer. Keeping the Nanosuspension under the Brookfield viscometer at room temperature, set the rpm at 100, set the

spindle No-21 and obtained values are noted.

Scanning Electron Microscopy

Determination of surface morphology (roundness, smoothness, and formation of aggregates) of nanosuspension is carried out by scanning electron microscopy (SEM). Size of the nanoparticle, shape and surface of the particles in nanosuspension were determined by Scanning electron microscope (SEM). In this method of determination nanosuspension was first diluted with ultra pure water (1/5), and then a drop of the diluted nanosuspension was then directly deposited on a polished aluminium sample holder. Samples were dried in vaccum. The morphology of nanoparticles was observed at15 kV using a scanning electron microscope.

Particle size

Particle size and particle size distribution are the important parameters since it will affect the saturation solubility, any change in the particle size, it will lead to the changein the solubility and dissolution. Particle size determines the physiochemical behavior of the drug. Particle size can be determined by SEM analysis. Particle size distribution can be determined by photon correlation spectroscopy (pcs) or laser diffraction (LD). Particlesize distribution is expressed as the polydispersity index (pi).pi value of 0.1- 0.25 indicates fairly nanosize distribution whereas its value greater than 0.5 indicates a very broad distribution.

Surface charge (zeta potential)

Zeta potential is determined by the stability of nanosuspension. A minimum zeta potential of 30 mv is required whereas, in case of combined electrostatic or stericstabilizer, a zeta potential of 20 mv would be sufficient.

pH

pH of the formulation was measured using a digital pH meter. The determination of the pH is done by using the glass electrode. The glass electrode is a dip into the solution and notes down the reading which showing in the display.

In-vitro diffusion study

In-vitro diffusion study was performed in order to find the percentage of drug release in phosphate buffer of all prepared formulations as well as the pure drug. The cumulative drug release of pure drug and other formulation can be found through this method. The diffusion study was performed in the franz diffusion cell with the 0.1 N HCL as a buffer media.

Stability studies

Stability of a pharmaceutical preparation can be defined as 'the capability of a particular formulation in a specific container/closure system to remain within its physical, chemical, microbiological, therapeutic and toxicological specifications throughout itsshelf life'. The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under influence of a variety of environmental factors such as temperature, humidity and light and enables recommended storage conditions, re-test periods and shelf-lives to be established.

ICH specifications for stability study:

The optimized formula of Bromhexine Hydrochloride nanosuspension were packed in amber coloured bottle packing and stored under the following conditions for a period of 3 months at 20-25 ºC ± 2ºC/75%.

Determination of sedimentation rate

Sedimentation volume is a ratio of the ultimate volume of sediment (Vu) to the originalvolume of sediment (VO) before settling.

RESULTS AND DISCUSSIONS

Pre formulation studies
Determination of Solubility

Table 4: Data of Solubility of drug

MEDIUM	SOLUBILITY
Water	Slightly Soluble
Ethanol	Soluble (1:1)
Methanol	Soluble (1:1)
0.1N Hydrochloric Acid	Soluble (1:1)

IR Spectroscopy of Drug
The IR spectra of pure drug

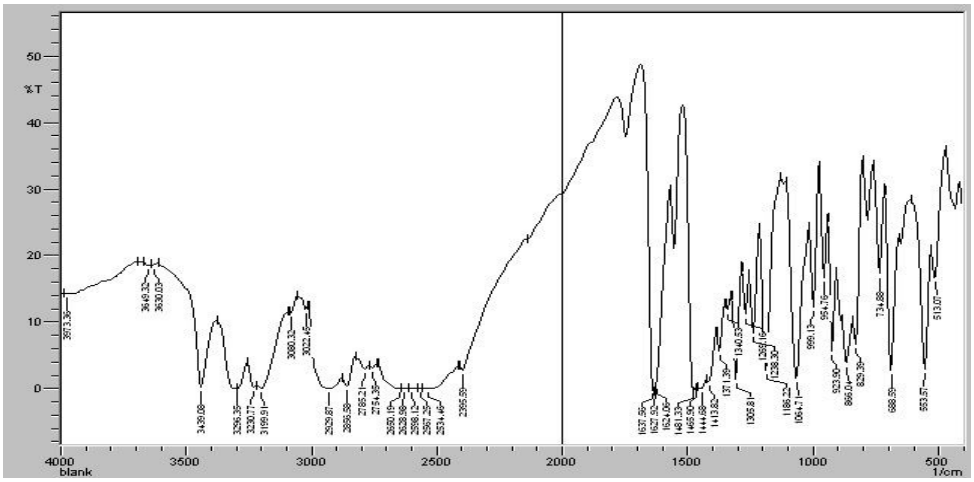

Fig 2: IR Spectra of Bromhexine HCL

Table 5: IR Spectral data of Bromhexine HCL

Compound name	Functional group	Standard range (cm^{-1})	Observed peak(cm^{-1})
Bromhexine HCL	C-H stretch (aromatic)	3150-3050	3022.45 3080.32
	C-H bending (aromatic)	2000-1660	1720
	N-H	1600	1624.05
	C=C stretch	1600-1480	1481.33
	C-N stretch	1350-1000	1340.53
	C-Br	600-500	513.07 553.57

Determination of pH
pH of the formulation was measured using a digital pH meter. The determination of the pH is done by using the glass electrode. The glass electrode is a dip into the solution and notes down the reading which showing in the display.

Table 6: pH of the nanosuspension.

Sl/No	Formula	pH range
1	F1	7.3±0.02
2	F2	7.1±0.01
3	F3	7.4±0.04
4	F4	7.3±0.03
5	F5	7.3±0.02
6	F6	7.2±0.01
7	F7	7.2±0.02
8	F8	7.4±0.02

** Mean (X ± S.D) (n = 3)*

pH of the optimised formulation was found to be 7.3±0.03

In-vitro drug release studies of F1-F4

Table 7: Percentage in-vitro drug release of formulations (F1-F8)

Time (Hr)	F1	F2	F3	F4
1	10.5±2	9±0.45	7.5±1.2	9±1.2
2	17.90±1.5	15.05±0.22	18.04±1	13.55±0.2
3	24.00±0.6	21.13±0.5	24.14±0.5	21.12±1
4	32.69±0.5	33.25±1.2	33.27±0.6	28.74±1
5	45.02±1	40.93±1	39.45±0.3	36.4±1.2
6	56.96±1.1	53.15±1.6	51.67±0.1	44.1±0.5
7	66.28±0.8	63.95±1	59.45±0.2	53.34±1
8	74.45±0.3	70.3±0.5	65.78±1	62.63±0.2
9	82.78±0.5	78.18±0.2	73.64±1.2	68.97±0.4
10	87.78±1.2	84.60±±0.2	80.04±1.1	73.85±0.2
11	91.23±1	88.06±1	86.47±1.1	78.75±0.5
12	89.94±0.5	92.14±1.1	94.55±0.45	82.02±1.5

Time (Hr)	F5	F6	F7	F8
1	12±1	10.5±0.23	9±0.51	7.5 ±0.2
2	19.50±0.32	18.05±0.3	16.55±0.5	15.04±1
3	27.4±1.2	24.15±1.1	24.14±0.12	19.62±0.5
4	36.55±0.5	31.91±0.21	34.77±0.32	25.73±0.6
5	49.75±0.2	39.45±0.65	40.96±0.8	31.42±0.8
6	56.99±1.1	47.11±0.3	50.19±1	38.04±0.21
7	67.26±1	57.95±0.24	56.46±1.3	47.25±0.62
8	76.56±0.51	71.71±0.4	64.27±0.7	59.51±0.15
9	85.95±0.6	78.13±0.8	72.12±0.3	65.83±0.23.
10	89.38±0.36	86.08±1.2	78.51±0.23	73.69±0.62
11	91.23±1	89.55±0.11	83.44±0.65	79.94±0.65
12	93.66±0.5	91.52±0.31	87.19±1	82.03±1.2

** Mean (X ± S.D) (n = 3)*

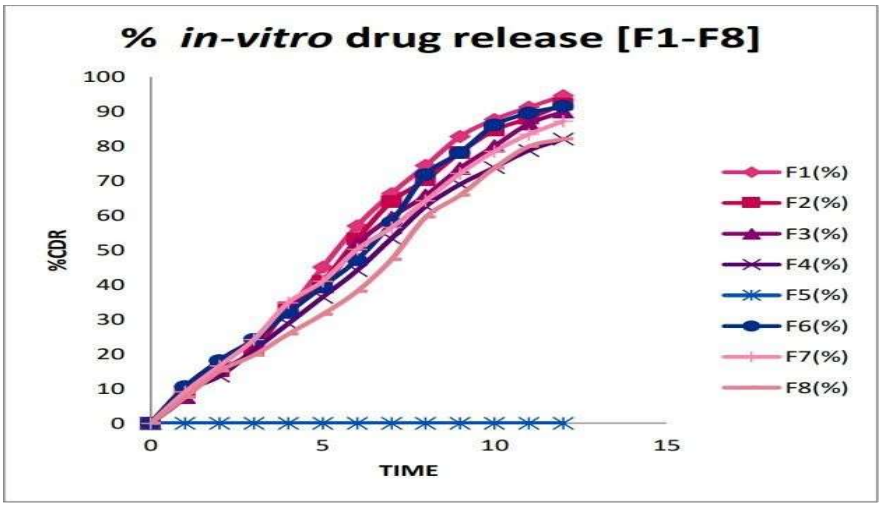

Fig 3: In-vitro drug release of formulations (F1-F8)

Stability studies

The optimized Bromhexine HCL F3 was introduced to the Stability studies up to the 3 month at the Room temperature. It shows the drug release and drug content. It shows the effect on the Diffusion study at the Room temperature initially 89%, after 1 month it showed the 86%. After 2 months it shows 83% and after 3 month the value is 83% showed. In the effect of the drug content at the Room temperature initially 92%, after 1 month it showed the 89%. After 2 months it shows 87% and after 3 month the value is 85% showed. The stability studies indicate that the nanosuspension is stable in a room condition.

Determination of sedimentation rate

Sedimentation volume is a ratio of the ultimate volume of sediment (Vu) to the original volume of sediment (VO) before settling. When F > 1 or Vu > Vo Sediment volume is greater than the original volume due to the net- work of flocs formed in the suspension and so loose and fluffy sediment

F = V u / VO

Where, Vu = final or ultimate volume of sediment VO = original volume of suspension before settling.

The purpose of this study was to formulate and evaluate the Bromhexine Hydrochloride nanosuspension by using high speed homogenization method. Bromhexine hydrochloride is a mucolytic agent (expectorant) used in the treatment of respiratory disorders associated with viscid or excessive mucus. The active ingredient Bromhexine hydrochloride is an expectorant which works by loosening mucus in the chest, making it easier to cough up secretions. It is also used to treat productive, chesty coughs.

Preformulation test

Determination of solubility

The solubility of Bromhexine Hydrochloride shows that it was slightly soluble in water, soluble in ethanol, methanol and 0.1N Hydrochloric acid as shown in Table 6.1.

Determination of melting point

The melting point of Bromhexine Hydrochloride was determined by Thiele's tube method and it was found to be 246±2 ºC (Table 6.2). The value obtained is within the standard range of values of 244-248ºC (Table 6.2).

Determination of Retention Factor by Thin Layer Chromatography

The retention factor of Bromhexine Hydrochloride by thin layer chromatography was found to be 0.75(Table 6.3).The value obtained is within the standard range ofvalues of 0.65-0.75(Table 6.3).

Determination of λ-max by UV Spectrophotometer

The λ-max of Bromhexine Hydrochloride was found to be 248nm (Table 6.4). The UV-Visible spectrum is shown in Fig 6.1. The value obtained is same to that of the British Pharmacopoeia.

R Spectroscopy of Bromhexine HCL

The IR spectrum of Bromhexine Hydrochloride was recorded by FT-IR spectrophotometer as shown in Fig. 6.2. From the peaks observed, it was seen that the functional group peak frequencies were in resemblance to the standard range values of Bromhexine Hydrochloride (Table 6.5). Thus, the presence of Bromhexine Hydrochloride can be confirmed.

Differential Scanning Calorimetry (DSC) of Bromhexine HCL

DSC thermogram showed a sharp endothermic peak at 247.70ºC which is corresponding to the melting point of the drug (Fig. 6.3). This value is between the standard range of 244-248ºC. Thus, the presence of Bromhexine Hydrochloride can be confirmed.

Powder X-Ray Diffraction (PXRD)

The crystals of Bromhexine HCl are orthorhombic. The cyclohexane ring has a normal chair form and the benzene ring is planar. There are three independent hydrogen bonds in the structure.

Drug-Polymer/Excipient compatibility

FTIR spectrophotometer

The individual IR spectrum of drug, HPMC K15M, Eudragit RS100, Lecithin, and Tween -80 were performed respectively. Then the IR spectrum of Bromhexine Hydrochloride was compared with the polymer HPMC K15M, Eudragit RS100, Lecithin,) and Tween -80 From the peaks observed, it was seen that the functional group peak frequencies of Bromhexine Hydrochloride were in resemblance to the reported range of the polymer Thus, they were compatible with each other.

Differential Scanning Calorimetry (DSC)

DSC thermogram showed a sharp endothermic peak at 247.70 ºC which is corresponding to the melting point of the drug (Fig. 6.3). DSC thermogram of HPMC K15M showed a sharp endothermic peak at 93.73 ºC and 221.88 ºC. The DSCof Bromhexine HCl and HPMC K15M showed a sharp endothermic peak at 75.88 ºC and 238.82 ºC. From the values obtained, there is a slight broadening and shifting ofan endothermic peak due to melting effect. Thus, they were compatible with each other.

Physicochemical evaluation

The physicochemical evaluation studies were performed by using the parameterssuch as estimation of saturation solubility studies, %Drug content, drug entrapment efficiency, viscosity measurements, zeta potential measurement, scanning electronmicroscopy, in vitro drug release and kinetic model studies.

Stability Studies

The optimized Terbutaline sulphate and Ambroxol Hydrochloride F2 was introduced to the Stability studies up to the 3 month at the Room temperature. The optimized formulaof Bromhexine Hydrochloride nanosuspension were packed in amber coloured bottle packing and stored under the following conditions for a period of 3 months 25 ºC ± 2ºC/75% and RH ± 5% RH. It show the effect on the Diffusion study at the Room temperature initially 89%, after 1 month it showed the 86%. After 2 months it shows 83% and after 3 month the value is 83% showed. In the effect of the drug content at the Room temperature initially 92%, after 1 month it showed the 89%. After 2 months it shows 87% and after 3 month the value is 85% showed. The stability studies indicate thatthe nanosuspension is stable in a room condition.

Determination of sedimentation rate

Sedimentation volume is a ratio of the ultimate volume of sediment (Vu) to the original volume of sediment (VO) before settling. When F > 1 or Vu > Vo Sediment volume is greater than the original volume due to the network of flocs formed in the suspension andso loose and fluffy sediment. This nanosuspension shows as flocculated and sedimaentation rate was high and not forming hard cake.

SUMMARY AND CONCLUSION

The present study was undertaken with an aim to formulate, develop and evaluate nanosuspension of Bromhexine Hydrochloride by using high speed homogenizer technique where the drug is released in a sustained manner for a period of 12hours. The different polymers namely HPMC K15M and Eudragit RS100 were used in different ratioand also the ratio of lecithin was varied in the preparation of nanosuspension. The identification of the drug was done using solubility, melting point, thin layer chromatography, UV-Visible, FTIR and DSC. All the analyses results successfully confirmed the identity of the Bromhexine Hydrochloride. The drug-polymer/excipients compatibility was performed using FTIR and DSC. FTIR results show that the Bromhexine

Hydrochloride is compatible with the HPMC K15M, Eudragit RS100, Lecithin, Tween 80.

The nanosuspension were prepared by high speed homogenizer method and evaluated for drug entrapment efficiency, drug content test, pH measurement, viscosity measurements, zeta potential measurement, scanning electron microscopy, in-vitro drug release and kinetic model studies. The optimum amount of HPMC K15M, Eudragit RS100, Lecithin, Tween80 is important in achieving good in-vitro drug release. The amount of HPMC K15M, EudragitRS100 and lecithin increases, the drug releasing time decreases because the drug was coated with stabilizer and polymer.

Formulation F3 with hydrophilic polymer HPMC and stabilizer (soya lecithin) in the ratio 1:1.5 (approx.) was considered as an optimised formulation. The optimised formulation show satisfactory sustained drug release at the 12th hrs. The stability studies of the nanosuspension indicate that it was stable in room condition. The nanosuspension of Bromhexine HCI successfully formulated by using High speed homogenizer. It can be increase solubility and drug release time and thereby improving its bioavailability.

From the present study, the following conclusions can be drawn:

1. Nanosuspension of Bromhexine Hydrochloride was good with the in-vitrodiffusion study.
2. Infrared spectroscopic and Differential Scanning Calorimetric studies indicated thatthe drug is compatible with the polymers and excipients.
3. For proper solubility and in vitro release, the polymer and stabilizer must be usedin the proper ratio.
4. Formulation F3 shows comparatively good in-vitro drug release profilr, drug
5. content, optimum particle size, good stability than the other formulations.
6. The prepared nanosuspension have a good solubility and drug releasing time thereby enhancing properties leading to its increased bioavailability.
7. Administration of the nanosuspension of Bromhexine Hydrochloride has beenreported that its diffusion almost ceases because of the low solubility. The oral bioavailability of Bromhexine hydrochloride is 20%. Advantages of nanosuspension of Bromhexine Hydrochloride will surely enhance the patient compliance and improve bioavailability.

REFERENCES

1. Venkatesh T, Nanosuspensions: Ideal approach for the drug delivery of poorly water soluble drugs, der pharmacia lettre, 2011;3(2); 203-213.
2. Papdiwal A, Pande V, Sagar K. Design and characterization of zaltoprofen nanosuspension by precipitation method. Der Pharma Chem. 2014;6(3):161–168.
3. Meera R, Devi P, Muthumani P, Sundari KJ. International journal of biological & pharma- ceutical research. 2013;4(5):386–9.
4. Wong JC, Doty MJ, Rebbeck CL. Microprecipitation method for preparingsubmicron sus- pensions. US Patent no.6: 2003, 607-784.
5. Irene P, Ruggero B, Ferdinando G. Solid-state chemistry and particle engineering with supercritical fluids in pharmaceutics, European journal of pharmaceuticalsciences 27,2006, 299–310.
6. Gora, ShayanaMustafaNanosizing of valsartan by high-pressure homogenization toproduce dissolution enhanced nanosuspension: Pharmacokinetics and pharmacodynamic study. Drug Delivery 2016;23(3);940-950.
7. Kalpesh S. Wagh, Satish K. Patil, Anup K. Akarte, Dheeraj T. Baviskar, Nanosuspension - A New Approach Of Bioavailability Enhancement, InternationalJournal of Pharmaceutical Sciences Review and Research, 2011;8(2);61-65.
8. Verma KAK, Nanosuspensions: Advantages and disadvantages, indian journal ofnovel drug delivery, 2012;4(3);179-188.
9. Hak-Kim Chan, Philip Chi Lip Kwok, Production methods for nano drug particles using the bottom-up approach, Advanced Drug Delivery Reviews 2011;63 (6) 406–416.
10. K.P. Karadag, Ayse Ozcelik Quercetin nanosuspensions produced by highpressure homog- enization Journal of Agricultural and Food Chemistry 2014;62(8);1852- 1859.
11. Sharma S, Issarani R, Nagori BP. Effect of solvents on particle size of aceclofenac nanosuspension prepared by bottom up technique. World J Pharm Pharm Sci[Internet]. 2015;4(4):1022–34
12. Maya George , Indrajit Ghosh, Identifying the correlation between drug/stabilizer prop- erties and critical quality attributes (CQAs) of the nanosuspensionformulation prepared by wet media milling technology, European Journal of PharmaceuticalSciences2013;48 (1-2) 142–152.
13. Patil SA, Rane BR, Bakliwal SR, Pawar SP. Nanosuspension: At a glance. Int J Ph Sci. 2011;3(1);947-960.
14. Bhowmik, DebjitHarish, GDuraivel, S Kumar, Nanosuspension -A Novel Approaches In Drug Delivery System2012;1(12)50-63.
15. Ahuja BK, Jena SK, Paidi SK, Bagri S, Suresh S. Formulation, optimization and In-vitro In-vivo evaluation of febuxostat nanosuspension. Int J Pharm. 2015;478(2);540– 52.

16. an Mo¨schwitzer, Georg Achleitner, Herbert Pomper, Rainer H. Muller, Development of an intravenously injectable chemically stable aqueous omeprazole formulation using nano- suspension technology, european journal of pharmaceutics, and biopharmaceutics 2004;58(3); 615–619.
17. Venkatesh T, Nanosuspensions: Ideal approach for the drug delivery of poorly water solu- ble drugs, der pharmacia lettre, 3(2), 2011, 203-213.
18. Kesisoglou, FilipposPanmai, Application of nanoparticles in oral delivery of immediate release formulations. Curr. Nanosci. 2007;3(2);183–190.
19. Lai F, Pireddu R, Corrias F, Fadda AM, Valenti D, Pini E, et al. Nanosuspension improves stretinoin photostability and delivery to the skin. Int J Pharm. 2013;458(1):104–109.
20. PanchaxariDandagi, ShashidharKerur, VinayakMastiholimath, Polymeric ocular for con- trolled release of acyclovir: in vitro release and ocular distribution, Iranian Journal of Pharma- ceutical Research 2009;8(2);79-86.