Original Article

Isoxsuprine Hydrochloride Loaded Cellulose Acetate Phthalate Microsponge Drug Delivery System: Design and Evaluation

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ABSTRACT

Aim: The present study was aimed to Design and evaluation of microsponge based drug delivery system of Isoxsuprine Hydrochloride. The microsponge drug delivery system is designed for site specific and controlled release of drug by using cellulose acetate phthalate to improve the site-specific absorption of drug. **Materials and Methods:** The microsponges was formulated by modified quasi emulsion solvent diffusion technique. The chemical interaction between Isoxsuprine Hydrochloride, cellulose acetate phthalate, ethyl cellulose and polyvinyl pyrrolidone was studied by FTIR, the results of FTIR it was confirmed that there were no chemical reaction in between drug and polymer. The compatibility study of drug and polymer were confirmed by DSC. **Results:** The results of FTIR it was confirmed that there were no chemical reaction in between drug and polymer. The *in vitro* drug release found in between range of 91.97% to 98.78% the highest % CDR was shown by formulation MS5. The optimized formulation (MS5) demonstrated favorable % entrapment efficiency (93.6%), % buoyancy (78%) and % cumulative drug release (98.78%). SEM revealed the release of Isoxsuprine Hydrochloride in controlled release pattern from spherical and porous microsponges. **Conclusion:** This study provides a new approach to formulate and evaluate the microsponges of Isoxsuprine Hydrochloride for treatment of premature labor during pregnancy.

Key words: Microsponges, Isoxsuprine Hydrochloride, Cellulose acetate phthalate, Quasi emulsion solvent diffusion, Site specific absorption.

INTRODUCTION

Administration of the drug through the oral route is most convenient, economical and common. Although the oral drug delivery system suffers from problem with absorption, short half-life as well as elimination. These problems can be avoided by formulating orally controlled release formulation for slow release of the drug into the gastrointestinal tract. This route can be easily utilized for the development of sustained and controlled release formulation of drugs. The oral route of drug delivery is most selective because of its economy, convenience and huge patient acceptance.[1]

The commonly used solid dosage forms are capsule and tablet; formulated nanoparticles, microparticles, microsphere, microsponge and nanospheres may be administered to a patient in the form of tablets and capsule. Microsponge drug delivery system is patented[2] highly cross-linked, porous, a polymeric system that can entrap a broad range of active ingredients and release them by enhancing performance.[3] Microsponges are mostly used for topical controlled release drug delivery system, but recently it can be used for oral drug delivery with solid dosage forms like tablet and capsule. Microsponge drug delivery system offers delivery of drug with a minimum dose, enhanced stability, least side effects and controlled release of the drug.[4] Polymers

Submission Date: 21-09-2019;
Revision Date: 26-12-2019;
Accepted Date: 12-03-2020

DOI: 10.5530/ijper.54.2s.73

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used in microsponge can entrap for benefits such as enhanced product efficacy, tolerability and mildness. Although the size of microsponge may vary from 5-300 µm, typical 25µm sphere can have up to 250000 pores. Now a day microsponge delivery System is used in cosmetics, over-the-counter (OTC) skin care, sunscreens and prescription products. There are several advantages of microsponge like stability at the pH range 1-11, stable at the temperature up to 130°C, compatible with most of the vehicle and active ingredients, the average size of microsponge pore is only 0.25µm and cost-effective.[5-7]

IUPAC nomenclature of Isoxsuprine Hydrochloride is 1RS, 2SR)-1-(4-hydroxyphenyl)-2-[(1RS)-1-methyl-2-phenoxyethylamino] propan-1-ol hydrochloride.[8] Isoxsuprine hydrochloride is an orally effective long-acting β - receptor stimulant which has direct smooth muscle relaxant property. It has been used as uterine relaxant for threatened abortion and dysmenorrhea.[9] Several attempts were made to formulate microsponge drug delivery systems by different method of preparation like emulsion solvent diffusion method[10] and quasi-emulsion solvent diffusion method[11] for Fluconazole[3] Ketoprofen[12] Benzoyl peroxide[10] Flurbiprofen[11] Meloxicam[13] Metronidazole[14] Lansoprazole,[15,16] Flurbiprofen,[17] Curcumin,[18] Dicyclomine[19] Oxybenzone.[20]

In the present work Quasi-emulsion technique was implimented for formulation of microsponge drug delivery system of isoxsuprine hydrochloride. Optimized formulation was characterized using particle size analysis, differential scanning calorimetric analysis (DSC), Fourier transform infrared analysis (FTIR) and Scanning Electron Microscopy (SEM). The formulated batches were evaluated for product yield, particle size, drug content, entrapment efficiency, *in vitro* buoyancy and *in vitro* drug release. The obtained *in vitro* drug release data was fitted to empirical equations to understand the mechanism and kinetics of drug release.

MATERIALS AND METHODS

Materials

Isoxsuprine Hydrochloride I.P., was obtained as a gift sample from Jayco chemicals Industries, Thane. Cellulose acetate phthalate, ethyl cellulose, polyvinyl pyrrolidone, ethanol, chloroform, span 80, hydrochloric acid and potassium dihydrogen phosphate were procured from loba chemicals, Mumbai.

Method: Preparation of isoxsuprine hydrochloride Microsponge

Quasi-emulsion technique was implemented for the preparation of isoxsuprine hydrochloride microsponge. A meassured quantity of Isoxspurine hydrochloride, Ethyl cellulose and cellulose acetate pthale were added in in the ethanol and chloroform (organic phase). For the preparation of 1% (w/v) dispersion span 80 was added in above solution with continuous agitation.

The solution was uniformly emulsified in polymeric solution to prepared w/o emulation. Polyvinyl pyrrolidone was used for perparation of aqueous phase in a separate beaker, prepared emulsion (w/o) was emulsified in it. A magnetic stirrer was used for continuous string of this w/o/w emulsion for 8 hr. The dispersed droplets were solidified in the aqueous phase by solvent evaporation. The microsponge was filtered, dried at 60°C in the hot air oven and stored in a desiccator. For more detail refer to Table 1.

Evaluation

Preformulation studies of isoxsuprine hydrochloride

Identification

0.01% w/v solution of isoxsuprine hydrochloride in 0.1M Hydrochloric acid was analysed at the range of 230 nm to 360 nm. Two maxima observed at about 269 nm and 274nm with absorbance 0.73 and 0.72 respectively.

Solubility

An excess amount of isoxsuprine hydrochloride was dissolved in water in a volumetric flask with frequent shaking and sonicating for 1hr. The saturated solution was filtered through whatman filter paper and the filtrate was suitably diluted with distilled water and analyzed by spectrophotometrically (Systronics, Ahmedabad.) at 269 nm against a blank. The study was performed in triplicate.

Melting point

For the determination of melting point small amount of drug was taken in capillary tube closed at one end It was placed in melting point apparatus (lab intelligence appliances) and the melting point was corrected.

Infrared spectroscopy (IR) study

Bruker Alpha –T spectrophotometer was used to determine IR spectrophotometric study of drug and polymer. The selenium bromide method was used to study IR spectra of drug and polymer to rule out drug - excipients interaction n.

Evaluation of Microsponges

Particle size and Product yield

The optical microscope was used to determine the particle size. The mean particle size of more than

Table 1: Formulation of isoxsuprine hydrochloride microsponges by Quasi-emulsion method.

Formulation code	Isoxsuprine hydrochloride (mg)	Ethyl cellulose (mg)	Cellulose acetate phthalate (mg)	Polyvinyl pyrrolidone (mg)
MS-1	80	100	200	0.5
MS-2	80	100	400	0.5
MS-3	80	100	600	0.5
MS-4	80	100	200	1
MS-5	80	100	400	1
MS-6	80	100	600	1

300 particles were calibrated against calibrated ocular micrometer. Product yield of microsponges was calculated by dividing the weight of microsponges to the total amount of material used in the preparation of microsponges.

Drug content and entrapment efficiency

Isoxsuprine hydrochloride loaded microsponges of each batch equivalent to 10 mg of Isoxsuprine hydrochloride were weighed and powdered using glass mortar and 10 mg powder was taken in to a volumetric flask and extracted with 5 mL of acetone by vortexing. The sample was centrifuged at 2000 rpm for 10 min, then the solution was filtered and assayed spectrophotometrically at 269 nm by using double beam UV- Spectrophotometer (Systronics, Ahmedabad). Drug content was calculated by dividing the practical drug content to the theoretical drug content. Entrapment efficiency was determined by dividing the practically entrapped amount of drug to the total amount of drug.

In vitro buoyancy

In this test, the accurately measured quantity of microsponge 50 mg was spread on the surface of the beaker containing 100 ml phosphate buffer (pH 4.5) and 0.02% Tween 80 for wetting effect. The magnetic stirrer was used for continous stirreing of medium for 8hr. At the end number of floating microsponges were measured.

In-vitro drug release study

United states Pharmacopoeia (USP) dissolution testing apparatus 2 (Paddle type Electrolab USP TDL- 08L, India). was used for the *in vitro* extended release of isoxsuprine hydrochloride from microsponge by using treated dialysis membrane. In this test 900 mL of simulated phosphate buffer having pH 4.5 was used as dissolution medium. The content was rotated at 50 rpm at 37 ± 1°C. A 5 mL sample of the solution was withdrawn from the dissolution medium initially and then regularly after 30 min interval up to 8 hr and analyzed drug release spectrophotometrically at 269 nm. All the readings were performed in triplicate.

Characterization of optimized formulation

Differential scanning calorimetry (DSC)

Differential scanning calorimetry (SDT Q600 V20.9 Build 20) was used for estimation of thermal behavior of isoxsuprine hydrochloride and optimized formulation (MS5) to identify the physical compatibility of drug with the polymer matrix. The samples were sealed in aluminum pans heated in an atmosphere of nitrogen and thermograms were obtained by heating at a constant heating rate of 10°C/min in the range of 0–300°C. A nitrogen purge (20 ml/min) was maintained throughout the run. The instrument was equipped with an intercooler to assess the thermal behavior of the sample. Alumina standard was used to calibrate the temperature and enthalpy scale of the instrument.

Scanning electron microscopy

Scanning electron microscope (Mira 3 TESCAN) was used to visualize the surface morphology of pure drug and optimized formulation MS5. Photographs at definite time intervals from dissolution study were taken to predict the possible release pattern of drug delivery system before and after drug release.

RESULTS AND DISCUSSION

Preformulation study of isoxsuprine hydrochloride

In the preformulation study, the physical and chemical properties of drug and polymer were evaluated for the development of a drug carrier system in the view of its stability and bioavailability. Preformulation parameters are useful for detection of safety, efficacy, acceptability and stability of the product. The essential physicochemical properties of a drug like a solubility and melting point were determined and found to be in an acceptable range.

Identification

UV spectrophotometer (Systronics, Ahmedabad.) was used for the identification of isoxsuprine hydrochloride at λ_{max} 268.2 nm and 273.8 nm of which absorbance were found to be 0.71 and 0.69 respectively.

Solubility

The solubility of isoxsuprine hydrochloride in distilled water found to be 1.9%w/v.

Melting point

The melting point of the drug was determined using melting point apparatus and the melting point was found 202°C.

Infrared spectroscopy (IR) study

The prominent peaks of isoxsuprine hydrochloride were observed in the region of 3362cm^{-1} due to the -OH stretching, a peak at 3292 cm^{-1} due to N-H stretching and a peak 3072 cm^{-1} due to aromatic C-H stretching. Peaks at 2981 cm^{-1} showed the presence of aliphatic C-H stretching,1577 cm^{-1} and 1454 cm^{-1} due to C=C aromatic stretching (Figure 1). The IR of a physical mixture of the drug with Ethyl cellulose and cellulose acetate phthalate showed the shape and location of peaks in the region 3362 cm^{-1} – OH stretching, a peak at 3292 cm^{-1} due to N-H stretching had noticeably changed. These suggest that drug interactions were absent (Figure 2).

Evaluation of Microsponges

Product yield

The product yield of microsponges was found in the range of 71.4% to 89.1% as shown in Table 2. From the experimental result, it is cleared that the product yield of microsponge is depended on the concentration of cellulose acetate phthalate and polyvinyl pyrrolidone. The highest yield of microsponge was found in formulation MS 6 (89.1%) where cellulose acetate phthalate (600 mg) and polyvinyl pyrrolidone (1 mg) were in the highest concentration. In contrast to this result lowest yield of microsponge was found in formulation MS1 (71.4%) at a low concentration of cellulose acetate phthalate (200 mg) and polyvinyl pyrrolidone (0.5mg) and which proved that the yield of microsponge is based on the concentration of cellulose acetate phthalate and polyvinyl pyrrolidone.[18] In addition to this, at a constant concentration of polyvinyl pyrrolidone, on increasing the concentration of cellulose acetate phthalate the product yield increased as explained by Lee *et al*. High level of cellulose acetate delays polymer precipitation by retarding the diffusion of organic phase to aqueous phase and provides more time for droplet formation.[21] whereas at another experimental condition low level of cellulose acetate phthalate forms less viscous organic phase which causes rapid mixing and faster removal of solvent and hence decreases the yield.

The increase in product yield was observed in formulation MS4, MS5 and MS6 due to the formation of large droplets at the high level of polyvinyl pyrrolidone.

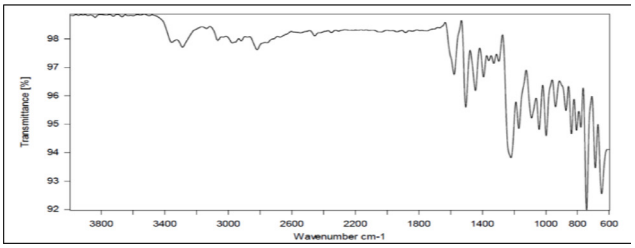


Figure 1: Infra-Red spectra of Isoxsuprine Hydrochloride.

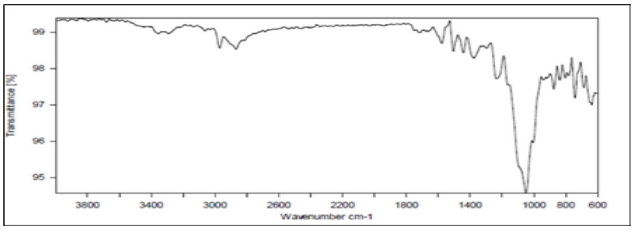


Figure 2: Infra-Red spectra of Isoxsuprine Hydrochloride + Ethyl cellulose + Cellulose acetate phthalate.

Particle size

The formulated microsponge of isoxsuprine hydrochloride having a size range in between 90.2 µm to 178.5 µm (Table 2). Formulation MS 6 exhibited a maximum particle size of 178.5 µm. The particle size of isoxsuprine hydrochloride loaded microsponge was found to be dependent on the concentration of the polymer.[22] The quantity of cellulose acetate phthalate governs the size of microsponge, an increase in the concentration of cellulose acetate phthalate increases the particle size. As the concentration of polyvinyl pyrrolidone increases, the formation of larger microsponge takes place due to the formation of large emulsion droplets which was observed in the formulations MS4, MS5 and MS6 where particle size was 106.5 µm, 130.5 µm 178.5µm respectively.

Drug content

Drug content for all the formulation was in the range of 79.1% (MS1) to 92.3% (MS5). MS5 formulation shows the highest drug content. For more detail refer Table 2.

Entrapment efficiency

The maximum entrapment efficiency was showed by formulation MS5 (93.6%) and the minimum entrapment efficiency was showed by formulation MS1 (80.7%). The entrapment efficiency increased up to a certain limit by increasing the concentration of cellulose acetate phthalate, but beyond the certain limit of cellulose acetate phthalate it decreased, at a constant concentration of poly vinyl pyrrolidone. The best entrapment efficiency was observed in formulation MS2 (91.5%) and MS5 (93.6%) (Table 2.) where the

Table 2: The Physicochemical Evaluation of Isoxsuprine Hydrochloride Microsponge.

Formulation code	Product yield (%)	Particle size (µm)	Drug content (%)	Entrapment efficiency (%)	Buoyancy (%)	Cumulative % Drug release
MS1	71.4	90.2	79.1	80.7	86	95.59
MS2	75.3	95.4	88.9	91.5	82	95.61
MS3	82.9	102.4	82.7	85.1	74	91.94
MS4	73.2	106.5	80.6	82.9	80	94.32
MS5	78.7	130.5	92.3	93.6	78	98.78
MS6	89.1	178.5	87.2	86.2	72	93.09

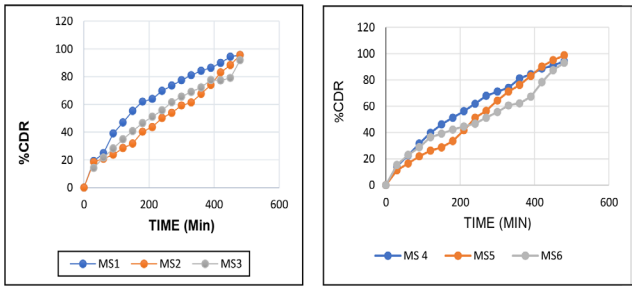
concentration of cellulose acetate phthalate and PVP were at an intermediate level. The high value of entrapment efficiency associated with the porosity of microsponges.

In vitro buoyancy

In vitro buoyancy studies revealed that the microsponges formed with a high level of cellulose acetate phthalate was having less buoyancy. The formulation MS6 showed the lowest buoyancy 72% with the highest concentration of cellulose acetate phthalate and poly vinyl pyrrolidone where as the formulation MS1 showed highest 86 % with the lowest concentration of cellulose acetate phthalate and poly vinyl pyrrolidone. (Table 2) As explained by V.S. Mastiholimath *et al.* at higher polymer concentration the relative density of microparticles was higher and it has less porosity.[23] In our studies, less buoyancy were found in microsponges having higher polymer concentration and higher buoyancy was found in microsponge with low polymer concentration. The results revealed microsponge with higher buoyancy found to be more porous than the microsponge with lower buoyancy.

In vitro drug release

The cumulative percentage drug release (% CDR) of isoxsuprine hydrochloride after 8 hr. was found between the ranges of 91.97% to 98.78% the highest % CDR was shown by formulation MS5. (Table 3) The *in vitro* drug release data revealed the polymer dependent drug release, the formulation with the low concentration of cellulose acetate phthalate showed the better release of drug as compared to the formulation with high concentration of cellulose acetate phthalate. The release data showed the 'burst release' of formulation MS1 at 2 hr. it showed the percentage release of drug 47.06% this bulk release of drug occurred due to the low concentration of cellulose acetate phthalate and presence of drug near to surface of microsponge. Formulation MS5 showed better % CDR, as it was having intermediate concentration of cellulose acetate phthalate and polyvinyl pyrrolidone which allowed release of drug in controlled pattern, it can also be correlated with the particle size of microsponge, as explained by Geetika Wadhwa *et al.*[24] The microsponge with large particle size are having less % CDR and microsponge having small size show the greater % CDR because it has the greater surface area than large microsponge. The data obtained from *in vitro* drug release was plotted on a graph (Figure 3a and 3b.) by taking time on X-axis and % CDR on the Y-axis



(3a) (3b)

Figure 3: *In vitro* drug release of microsponge formulations 3a. MS1, MS2 and MS3, 3b. MS4, MS5, MS6.

Table 3: Percentage cumulative drug release (%CDR) of Isoxsuprine Hydrochloride loaded microsponges.

Formulation code	Time in h.							
	1	2	3	4	5	6	7	8
MS1	24.30	47.06	61.99	69.71	77.46	84.24	89.93	95.59
MS2	20.79	28.51	40.26	50.14	59.14	67.57	83.09	95.61
MS3	15.11	34.71	46.60	55.77	65.67	72.20	77.33	91.94
MS4	22.68	39.77	51.28	61.90	71.18	81.18	88.76	94.32
MS5	16.42	26.24	33.47	51.18	64.39	76.20	90.32	98.78
MS6	21.98	36.35	42.28	46.78	55.53	62.23	78.29	93.09

Kinetic modeling of microsponge formulation

The *in vitro* drug release data of isoxsuprine hydrochloride loaded microsponge was subjected to various release models like Higuchi, Korsmeyer-Peppas, zero order and first order and the best fit model was decided by highest R^2 values.The highest R^2 values were shown by Higuchi, so the best model for optimized formulation was Higuchi[25] The highest R^2 values were observed in the Higuchi model (0.9970 for MS5), by the highest R^2 values 0.931 Fickian diffusional releases occurs by the general molecular diffusion of the drug due to a chemical potential gradient. The Korsemayer-Peppas plot of MS5 formulation showed a Fickian release pattern with correlation coefficient of $R^2 = 0.931$. The Figure 4 a, b, c and d. Showed graph of the optimized formulation after comparing the various kinetic models.

DSC Analysis

Initial slight endothermic bend was observed in DSC of isoxsuprine hydrochloride (Figure 5) at 85.33°C afterward a sharp endothermic peak begins at 213.84°C which was probably due to melting of Isoxsuprine Hydrochloride (M.P-203°C). This peak was observed until 223.79°C. Then system stopped absorbing heat this might be due to melting of total drug The (Figure 6) explains about DSC thermogram of MS 5 formulation although it has shown endothermic peak at lower temperature 82.95°C the peak is broad and not sharp and the calorie consumption at this temperature is much higher than that of isoxsuprine hydrochloride thermogram. Afterward, the DSC of formulation shows a slight peak at 163.51°C and 177.49°C and then the peak is shifted towards high temperature 199.28°C to 215.63°C even no significant change in temperature of the drug was observed with the MS5 formulation so, isoxsuprine hydrochloride is found to be compatible with the polymers used in this formulation.

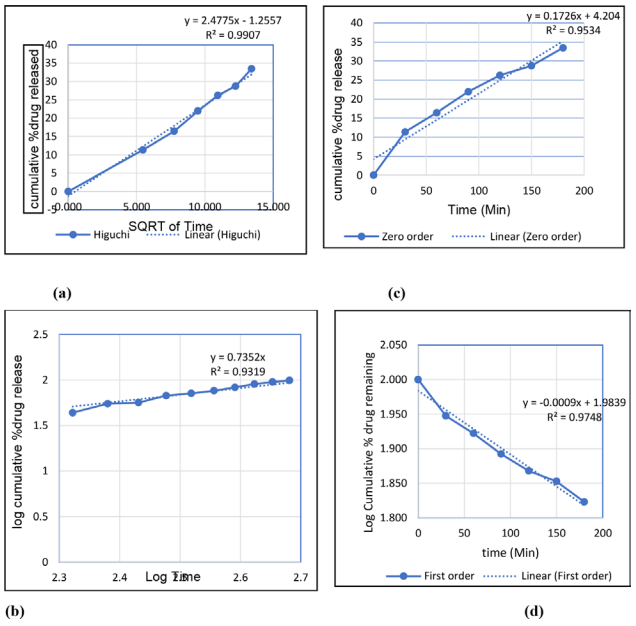


Figure 4: Kinetic modelling of optimized microsponge formulation MS 5 a. Higuchi release model, b. First order, c. zero order and d. Kors– Peppas.

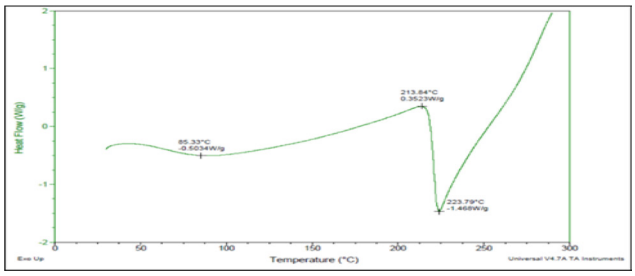


Figure 5: Differential scanning calorime try Isoxsuprine Hydrochloride.

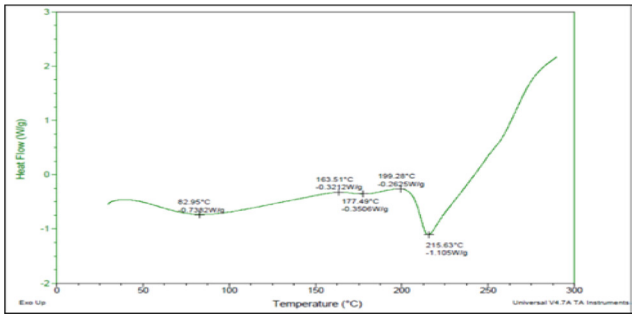


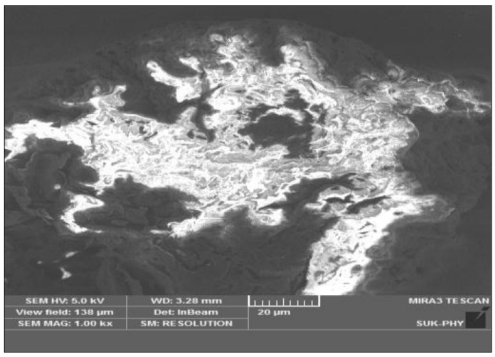
Figure 6: Differential scanning calorimetry of optimized Formulation MS5.

SEM Analysis

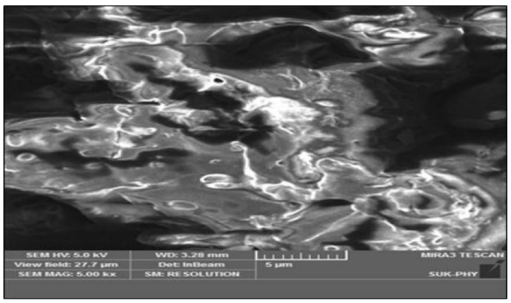
SEM Analysis was carried out to determine surface morphology of the formulations before and after the drug dissolution from the optimized (MS5) formulation. This study revealed that change in the surface morphology of MS5 formulation from 4 hr to 8 hr. in dissolution medium shown in Figure 7 (a, b and c). The erosion of polymer of microsponge is clearly observed in (Figure 7 d) after 8 hr. Hence, we can say that there is swelling as well as erosion mechanism involved in this drug delivery system.

CONCLUSION

Microsponge as a drug delivery system is evolving technology having broad application in the field of pharmaceutical manufacturing. Microsponges are porous microparticles having the ability to release the drug in a controlled manner; it can be productively used in targeting the drug to their desired sites of action.



(a)



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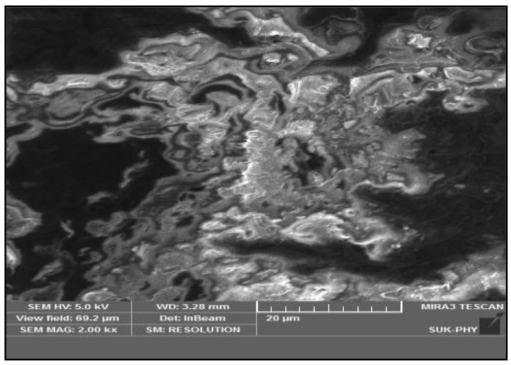
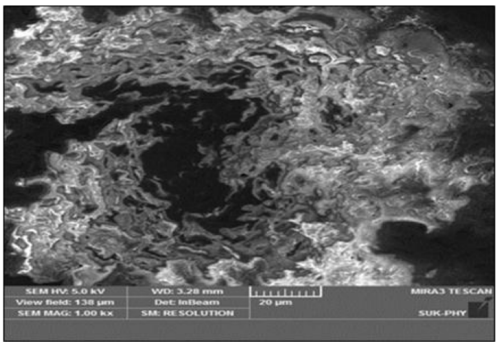


(c)



(d)

Figure 7: Surface Morphology of optimized formulation MS 5 a. entrapment of drug in porous of microsponge b. Release pattern of drug from microsponge after 2h of dissolution studies, c. Release pattern of drug from microsponge after 4h of dissolution studies and d. Release pattern of drug from microsponge after 8h of dissolution studies.

Thus, microsponges are utilized as a drug delivery system for targeted and controlled release of different oral, topical and site-specific drug delivery system

The microsponge particles have the ability to adhere to the surface of intestinal mucosa so, it is applied for local drug delivery. Preparation methods of microsponge are adjustable according to drug-polymer ratio; which is proved to be as safe and stable drug delivery system for oral and topical drug delivery system.

The model drug isoxsuprine hydrochloride used in the present study having the vasodilator activity. It is also used as smooth muscle relaxant of uterine. The positive results from this study can be utilized for formulation novel drug delivery of isoxsuprine hydrochloride at industrial scale.

ACKNOWLEDGEMENT

The authors would like to thank SVERIs College of pharmacy, Pandharpur for providing the research facility. Authors would also like to thanks Jayco Chemicals Industries, Thane for providing the gift sample of drug Isoxsuprine Hydrochloride.

CONFLICT OF INTEREST

The authors will declare no conflict of interest.

ABBREVIATIONS

OTC: Over the counter; **FTIR:** Fourier-transform infrared Spectroscopy; **DSC:** Differential scanning calorimetry; **% CDR:** Percentage cumulative drug release; **SEM:** Scanning electron microscopy; **mg:** Mili gram; **h:** Hours.

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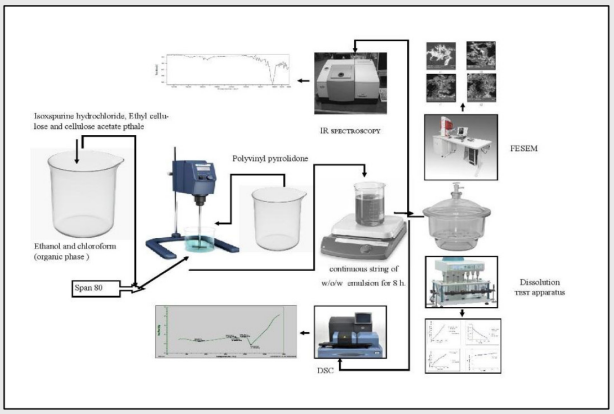
PICTORIAL ABSTRACT



SUMMARY

In the present study microsponge drug delivery system of Isoxsuprine Hydrochloride, a vasodilator used for smooth muscle relaxation to avoid the premature labor pain and dysmenorrhea. This formulation was prepared by using cellulose acetate phthalate, Poly vinyl pyrrolidone and ethyl cellulose.

Quasi-emulsion technique was implemented for the preparation of Isoxsuprine Hydrochloride microsponge.

The prepared batches of formulations were evaluated for FTIR, DSC, SEM and *in vitro* dissolution studies.

The results of this work reveals the applicability of microsponge as a drug delivery system for site specific absorption of drug by applying the listed polymers.

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Cite this article: Kagade S, Savjani J, Yadav D, Gurav P. Isoxsuprine Hydrochloride Loaded Cellulose Acetate Phthalate Microsponge Drug Delivery System: Design and Evaluation. Indian J of Pharmaceutical Education and Research. 2020;54(2s):s173-s181.