

RESEARCH AND REVIEWS: JOURNAL OF PHARMACEUTICS AND NANOTECHNOLOGY

Preparation and Evaluation of Wax Microparticulate for Sustained Release Drug Delivery System.

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Research Article

Received: 02/12/2013

Revised: 22/12/2013

Accepted: 30/12/2013

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Keywords: wax, sustained
release, microparticles, atenolol

ABSTRACT

Now a day's many lucrative novel drug delivery systems are developing at immense rate. One of them is Microparticulate drug delivery system. The present study envisages formulation of wax microparticulate drug delivery system. Congealable disperse encapsulation method is used to develop sustain release of Atenolol. The microspheres were prepared by varying the ratio of carnauba wax as sustained release agent at three levels mainly 8%w/w 9% w/w and 10%w/w. Tween 80 used as surfactant and varied as 1%w/v, 1.5% w/v and 2% w/v. The effects of these variables on particle size, morphology and drug release were evaluated. Encapsulation efficiency decreases as the concentration of polymer increases. The drug release from *invitro* study followed matrix model and it shows initial burst release followed by constant release up to 8 hrs. After oral administration it can be concluded that the use of wax for entrapment of atenolol is very promising way to sustain the release satisfactorily.

INTRODUCTION

Dosage forms that can precisely control the release rates of drug have made an enormous impact in the formulation and development of novel drug delivery systems. Recently, scientists are focusing on development of dosage form at nano and micro level. Microsphere is one of such dosage form. These are basically developed for controlled release of drug by using various polymeric materials [1,2,3,4]. The most significant features of microparticulates are microscopic size and more surface area. Through selection of optimum core and coating material we can explore the use of microsphere for variety of beneficial functions [5].

Waxes such as carnauba wax, bees wax spermaceti wax had been utilised for preparation of controlled release microparticles by means of melt dispersion or spray congealing techniques without the use of organic solvent [6]. Use of wax material found to have benefits such as inertness, low cost, ease of manufacturing. The advantages of waxes include good stability at varying pH and moisture levels, well established safe application in human due to their non-swellable and water insoluble nature, minimal effect on food in the gastrointestinal tract, and no dose dumping [7]. Carnauba wax is highest melting point wax contains esters of fatty acids, fatty alcohols and hydrocarbon. It has been reported to act as sustain release agent for variety of drugs such as Calcium Pectinate, Ibuprofen, Lamivudine, Lithium carbonate [8,9,10]. Atenolol is β -1 cardio selective adrenergic receptor blocker, widely used in the treatment of hypertension. The drug is insoluble in water and has half-life of 6-8 hours with oral bioavailability of 50% due to smaller dose of drug (less than 50 mg) [11,12].

Objective of the present investigation is formulation of wax microparticulate drug delivery system by Congealable disperse encapsulation method for sustain release of Atenolol. The microparticulates were prepared by varying the ratio of carnauba wax as sustained release agent at three levels mainly 8%w/w 9% w/w and 10%w/w. Tween 80 used as surfactant and varied as 1%w/v, 1.5% w/v and 2% w/v. The effect of these variables on particle size, Morphology and drug release was studied.

MATERIALS AND METHODS

Materials

Atenolol was obtained from Nicolas Piramal, Mumbai. All other reagents and chemicals used were of analytical grade.

Preparation of wax microparticulates

Weighed amount of carnauba wax was melted separately in china dish using water bath.

Atenolol previously passed through sieve no.100 was dispersed in the melted waxmass evenly and stirred to obtain a homogeneous melt. These individual mixtures were poured into 150 ml of distilled water, which was previously heated to a temperature higher than melting point of wax containing varying concentration of tween80. The whole mixture was mechanically stirred at 1200 rpm using a stirrer. Spherical particles are produced due to dispersion of molten wax in the aqueous medium. The mixture was stirred continuously at 900 rpm at a higher temperature of the melting point of wax for 5 min. The temperature of the mixture in the beakers was cooled rapidly to 10°C by the addition of cold water. The resultant solid spheres collected by filtration were extensively washed with water to remove any drug and surfactant residues. Air drying was carried out at room temperature for 48 h produced discrete, free flowing solid microparticulates. Total 9 formulations were prepared by varying concentration of wax and tween 80 as shown in table 1.

Table 1

Formulation code	Qty. of Wax (gm)	Drug (gm)	Tween 80(%)
F1	8	1	1
F2	8	1	1.5
F3	8	1	2
F4	9	1	1
F5	9	1	1.5
F6	9	1	2
F7	10	1	1
F8	10	1	1.5
F9	10	1	2

Evaluation Parameters

Particle Size Analysis of microparticulates ^[13]

Microsphere size determination was done by optical microscope. The suspension of the sample is prepared and then drop of resultant mixture is placed on the slide and observed through the eye piece.

Scanning Electron Microscopy ^[14]

The shape and surface characterization of microparticulates were observed under a Scanning Electron Microscope Model Joel- LV-5600, USA, at suitable magnification at room temperature. The photographs were observed for morphological characteristics and to confirm spherical nature of the microparticulates.

Angle of Repose ^[15]

Angle of repose was calculated by static method using funnel. The angle of repose (θ) is calculated by the following formula,

$$\theta = \tan^{-1} (h/r)$$

Where, h = pile height of microparticulates, r = radius of the circular are formed by the microparticulates on the ground.

Tap Density ^[15]

The Tap density was determined by tap density test apparatus. Weighed quantities of prepared microparticulates were filled in 10 ml of graduated cylinder the initial volume was noted. After tapping for the final volume was noted. The tap density was calculated as per following formula:

$$\rho = W_o / V_o$$

Where, ρ = Tap density, W_o =Weight of sample in gm, V_o = Final volume after tapping.

Drug Content ^[16]

Accurately weighed 100 mg microparticulates, crushed in glass mortar and pestle and the powdered microparticulates were suspended in 100 ml of 0.1N HCl. After 12 hours the solution was filtered and the filtrate was analysed for the drug content using UV -Visible spectrophotometer at 224nm.

Encapsulation Efficiency ^[17]

Encapsulation efficiency was calculated using the following formula

$$\text{Encapsulation efficiency} = \frac{\text{Estimated drug content}}{\text{Theoretical drug content}} \times 100$$

Fourier Transform Infrared Spectroscopy (FTIR)

FTIR spectra of pure drug, empty microparticles and drug loaded microparticles were obtained using powder diffuse reflectance on a FTIR spectrophotometer.

In-Vivo Dissolution Studies

Dissolution studies were carried out for all the formulations, employing USP XXIII apparatus (Basket method) at $37 \pm 0.5^\circ\text{C}$ rotated at constant speed of 50 rpm using 0.1N HCl as the dissolution medium for first 2 hrs.and remaining in phosphate buffer pH 6.8. A sample of microparticulates equivalent weight to 100 mg of Atenolol was used in each test. An aliquot of the sample was periodically with drawn at suitable time interval and the volumes were replaced with fresh dissolution medium in order to maintain the sink condition. The sample was analysed spectrophotometrically at 224nm.Release studies were carried out in triplicate.

RESULT AND DISCUSSION

For the preparation of microparticles of Atenolol tween 80 is used in varying concentration. Drug is sparingly soluble in water. The volume of water used is about 150ml if the reduced volume is not sufficient for the formation of microparticles. If the volume is reduced irregular shaped particles are found as well clumps are formed. Tween 80 is used as surfactant in varying concentration just to check effect on particle size and drug release. Without surfactant formulation is not possible. Speed is optimised at 1200 rpm below that speed particle size is increased.

Microsphere Size Analysis

Microsphere size determination was done by optical microscope. The mean particle was found in the range of 31.63 -96.6 μ . Results are shown in Table 2. Concentration of tween 80 plays important role in particle size distribution as per the experimental findings there is inverse relationship between particle size and concentration of tween 80. Size distribution plays a very important role in determining the release characteristics of the microparticulates.

Scanning Electron Microscopy

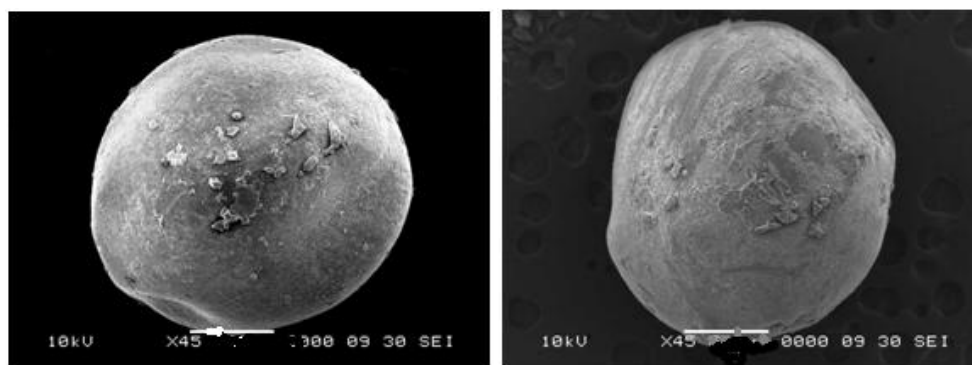


Figure 1: Shows shape and size of microparticles.

The shape and surface characterization of microparticulates were observed under a Scanning Electron Microscope (SEM). Optimised batch is selected for SEM analysis. Particles are having spherical shape and rough surface. Result is shown in Figure 1.

Angle of Repose

Angle of repose was calculated by static method using funnel. It is an indication of flow property. All the formulations show good flow property. Tap density and carr's index is found to be satisfactory. Results of all the formulations are shown in Table 2.

Drug Content and Entrapment Efficiency

Drug Content and Entrapment Efficiency was found in the range of 69-85%. As the drug is thoroughly mixed with the wax uniform distribution of the drug and entrapment takes place as well as drug is insoluble in water so release of the drug during preparation is avoided. Formulation F3 shows maximum entrapment efficiency. It is observed that as the concentration of polymer increases drug content decreases. Results of all the formulations are shown in Table 2.

Table 2

Formulation	% Yield (%w/w)	Mean particle size (Microns)	Angle of repose	Tap density	Carr's index	Drug Entrapment (%)	Drug content(mg)
F1	90.14	96.6 ± 1.4	20.64	0.227	5.78	78 ± 2.23	13.25
F2	94.11	61.13 ± 1.9	30.41	0.20	13.04	82 ± 2.75	15.22
F3	94.82	59.22 ± 2.1	25.24	0.227	13.24	85 ± 2.84	19.6
F4	91.22	98.57 ± 1.74	27.03	0.294	10.60	71 ± 2.45	16.24
F5	90.09	78.39 ± 1.58	21.33	0.357	12.54	69 ± 2.57	12.3
F6	92.27	60.17 ± 2.01	27.6	0.279	16.06	70 ± 1.21	16.5
F7	90.14	96.87 ± 2.42	24.14	0.246	13.66	81 ± 3.54	14.57
F8	93.54	80.24 ± 1.23	26.33	0.274	14.28	75 ± 1.57	15.02
F9	91.57	71.22 ± 1.64	24.12	0.247	15.08	71 ± 2.31	13.87

Fourier Transform Infrared Spectroscopy (FTIR)

An FTIR spectrum shows that both the drug and polymer are compatible with each other.

Figure 2. shows FTIR spectra of blank carnauba wax microparticulates, pure drug and formulation F3. IR spectra indicates that IR frequency bands of the -OH and H-N and groups having stretched at 3368 cm⁻¹ and 3198-3071 cm⁻¹ respectively are not affected in the presence of carnauba wax.

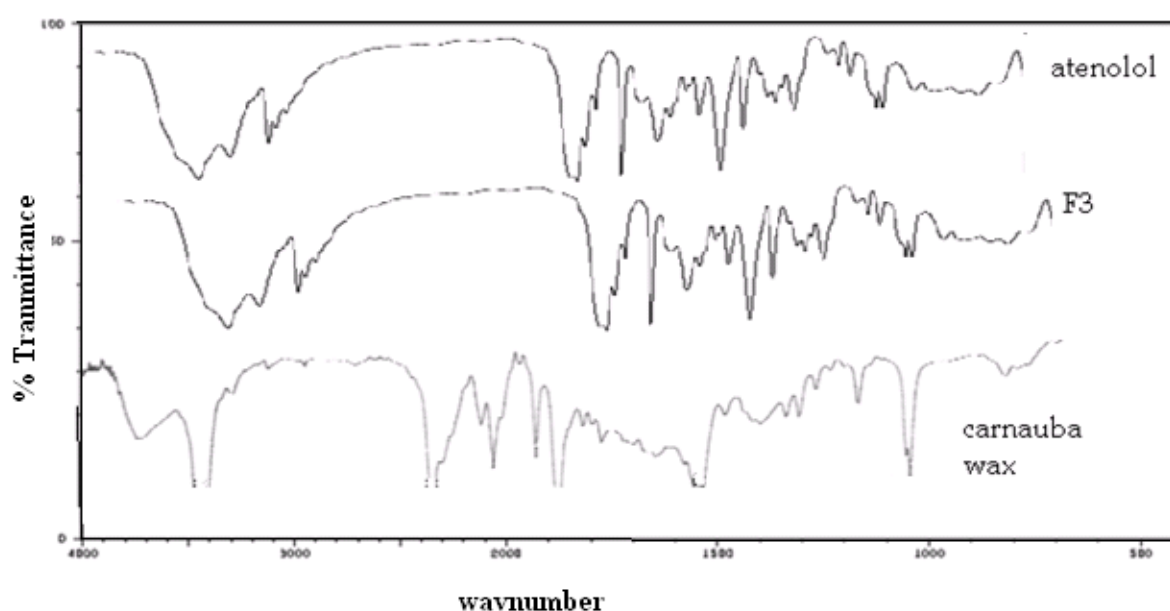
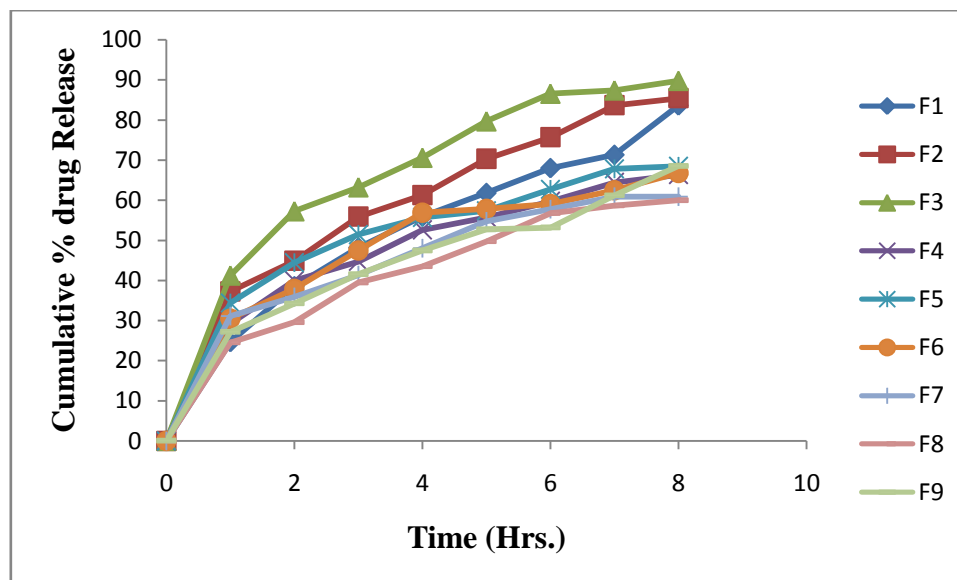


Figure 2: Shows FTIR spectra of pure drug, formulation and carnauba wax.

In-Vivo Dissolution Studies and Release kinetics

From the release studies it was observed that, formulation F3 shows extended release up to 8 hrs. There is initial burst release followed by constant release. When the concentration of carnauba wax decreases drug release decreases this is because more will be the wax concentration more time is taken to diffuse the drug molecule. Figure 3.

Figure 3: Drug release



CONCLUSION

From the above data it can be concluded that there is no vigorous treatment to the formulation so the yield of the product is optimum as well as particle size can also be optimised. As the concentration of tween 80 is increases particle size decreases and drug release increases. All the particles are having spherical shape. Formulation F3 contains 8 gm. of wax and 2% of tween 80 is able to retard the drug as defined in sustain release pattern. It releases the drug 89% upto 8 hrs. so it can be assumed that it can prolong the release upto 12 hrs.

ACKNOWLEDGEMENT

Authors are thankful to Modern College of Pharmacy (For Ladies), Moshi, Pune for providing necessary facility to carry out the research work.

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