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Research Article

MICROENCAPSULATION FOR PREPARING SUSTAINED RELEASE DRUGS

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ABSTRACT

The work comprises of formulation and evaluation of microencapsulated sustained release Isoxsuprine Hydrochloride tablets using different proportions of Ethylcellulose, Polyethylene glycol 6000 and Polyethylene glycol 4000 as the coat material. Phase separation technique was used with Cyclohaxane as the solvent. The prepared granules were found to be free flowing and spherical in shape. X-Ray diffractometer was used to determine the size of the granules and the thickness of the coating.

Tablets were prepared from stable granules. Parameters such as uniformity in thickness, friability, weight variation, hardness and the drug content of the tablets were evaluated. A six-stage dissolution test apparatus with phosphate buffer solution of 7.4P^H was used to study the drug release pattern. The First Order Plot, Higuchi plot and the Koresmeyer et al plot were drawn. It was observed that the prepared formulation followed the Higuchi plot. The mechanism for drug release has been suggested as Diffusion.

Keywords: Isoxsuprine Hydrochloride, Polyethylene glycol 6000, Polyethylene glycol 4000, Ethyl cellulose, Temperature change technique, X-Ray diffractometer.

INTRODUCTION

Development of novel drug delivery system has been one of the thrust areas of pharmaceutical research. Sustained release dosage forms were designed to release a drug at a predetermined rate by maintaining a constant drug level for specific period of time with minimum side effects. Sustained release micro encapsules gradually release therapeutic quantity of the drug in a constant manner. These can be prepared to yield high percent of drug at an economical cost[1].

The objective was to microencapsulate Isoxsuprine Hydrochloride by using various proportions of hydrophilic and lipophilic polymers such as Ethyl cellulose, PEG 6000 and PEG 4000. The prepared formulations were characterized for their physico-chemical properties[2].

MATERIALS

Analytical Grade chemicals were used for the experimentation. Isoxsuprine Hydrochloride was procured from Jagath Pharmaceuticals Ltd, Bangalore. PEG 6000 and PEG 4000 were procured from SD-Fine Chemicals, Mumbai. Ethylcellulose was procured from Loba –Chemie Pvt Ltd, Mumbai.

METHODS

Experimental procedure for tablet punching: Cocervation phase separation method was employed to formulate microcapsules. The polymer was dissolved in cyclohexane (solvent) by heating to 80^0c.

Finely pulverized drug was dispersed in the solution of polymer in cyclohexane with vigorous stirring at 200 rpm. After proper dispersion the contents were cooled slowly and gradually to affect phase separation. The product obtained after washing and drying was passed through a very fine sieve (# 250) to separate the individual microcapsules.

Sustained release tablets from the obtained microcapsules were prepared by direct compression such that each tablet contained 100mg of ISH. The microcapsules were blended with 1% gelatin, 1% talc, 1% magnesium stearate and starch. The mixtures of granules are compressed on a single station tablet punching machine.

The following Quality Control tests were carried out on the compressed tablets

Diameter and Thickness of tablets

The diameter and thickness of the tablets were measured by using a vernier caliper.

Uniformity of weight

10 tablets at random were taken and weighed. The average weight of tablets was calculated. Each tablet was also weighed individually and the weight noted. The weights of individual tablets were then compared with the average weight of the tablets.

Hardness

The hardness of the tablets was measured by using a Monsanto Hardness Tester. The tablet was placed between spindle [plunger] and the anvil. The knurled knob was then turned. The scale was adjusted to zero. The pressure on the tablet was increased by further turning the knurled knob until the tablet breaks. The force was read from the scale in kilograms.

Friability

The Friability was tested by using Roche Friabilator. The sample tablets were weighed accurately in a digital balance [W_1]. These tablets were weighed again after subjecting to friabilator [W_2]. The difference between the initial weight of the tablets [W_1] and weight of the tablets after subjecting to friabilator [W_2] gives the friability of the tablet.

Percentage of Medicament

A number of tablets from a batch were selected at random and assay procedures were carried out according to the monograph. For the assay, 500mg of Isoxosuprine Hydrochloride was taken accurately in a 1000ml volumetric flask and made up to the mark and the absorbance was noted.

This was compared with the standard solution of Isoxosuprine Hydrochloride [USP] at a wave length of 274nm [λ_{max}].

Rate of disintegration

Disintegration test was performed in-vitro using an in-vitro apparatus which consists of a basket and containing six open ended glass tubes which was held vertically between two transparent plastic plates. One tablet was placed in each glass tube and the whole assembly was placed in a one liter beaker filled with water, such that the tablet remains 2.5cm below the surface of the liquid on their upward movement and 2.5cm away from the bottom on their downward movement. Perforated plastic disc was placed in each of the glass tubes over the tablets to prevent them from floating. The temperature was maintained around 37±2°c by using a thermostat[4].

Dissolution Test [In-vitro release][8-9]

The apparatus for the dissolution test consists of:

A cylindrical stainless steel basket which was attached to the end of stirrer shaft. A 1000ml vessel made of glass was fitted with a cover having four holes, one for the shaft of the stirrer, second for placing the thermometer and the remaining two for removing the samples. A variable speed motor driven stirrer rotating at a speed of 25 revolutions per minute.

The temperature of the dissolution medium was maintained at a temperature of 37+/-0.5^0 c by a thermostatically controlled water bath [5,6]. The dissolution patterns are shown in graphs.

X-Ray Diffractometer

Powder diffraction [XRD] was the technique used to characterize the crystallographic structure, crystal size [grain size] and preferred orientation in polycrystalline or powdered solid samples. Powder diffraction was used to identify unknown substances, by comparing diffraction data against database maintained by the International Centre for Diffraction Data. An effect of the finite crystalline size was seen as a broadening of the peaks in an X-ray diffraction as explained by the Scherrer Equation[7].

RESULTS

The average diameter of all the tablets was found to be 9.5mm and the average thickness was found to be 3.5 mm.

The average weight of tablets was found to be 300 mg.

The average weight variation was found to be within +/-2%.

The hardness of the prepared tablets was found to be between 4.0 and 6.0 kg/cm^2.

The prepared tablets were found to have a friability value of 0.5 to 1% of their original weight[3].

The percentage of medicament was found to be within the range of 98% to100%.

The results for some of the above are indicated in the Tables 1, 2 and 3.

The thickness of the coat with PEG 6000 polymer =9.48199nm.

Table 1: Evaluation tests for ISH microencapsulated with PEG 6000

Characteristics	T-ISH1:1	T-ISH 1:2	T-ISH1:3
Uniformity of weight[mg]	298	306	305
Hardness of tablet [kg/cm^2]	4.8	5.2	5.4
Friability of tablet[%]	0.63	0.642	0.661
Disintegration of tablet[min]	60	75	100

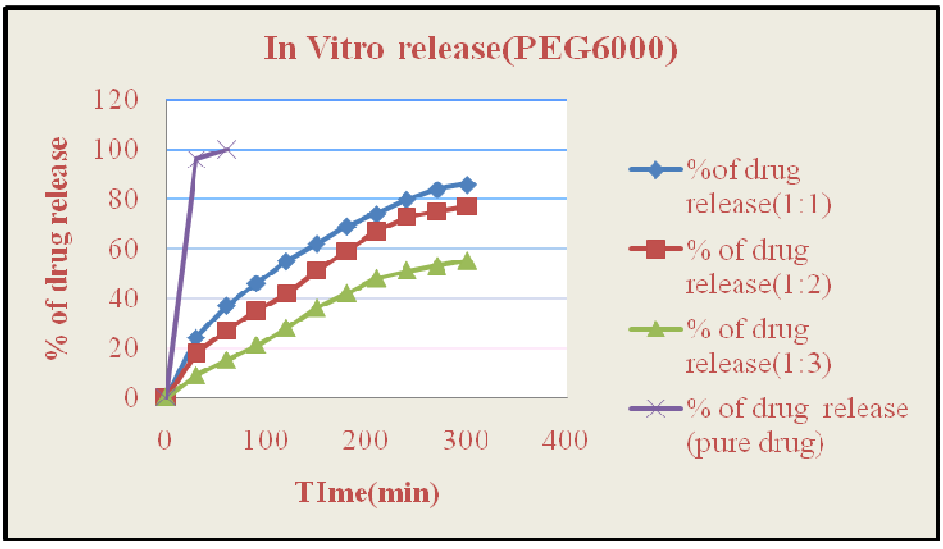
Table 2: Evaluation tests for ISH microencapsulated with PEG 4000

Characteristics	T-ISH1:1	T-ISH 1:2	T-ISH 1:3
Uniformity of weight[mg]	290	298	302
Hardness of tablet [kg/cm^2]	4.4	5.3	5.5
Friability of tablet[%]	0.54	0.551	0.57
Disintegration of tablet[min]	64	70	80

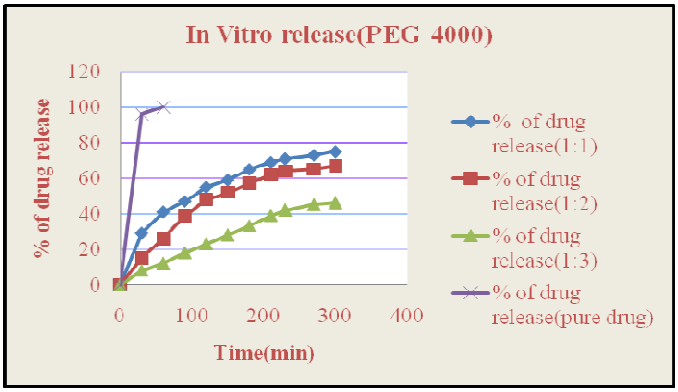
Table 3: Evaluation tests for ISH microencapsulated with Ethylcellulose

Characteristics	T-ISH1:1	T-ISH 1:2	T-ISH 1:3
Uniformity of weight[mg]	293	302	309
Hardness of tablet [kg/cm^2]	5.2	5.6	6.0
Friability of tablet[%]	0.512	0.535	0.55
Disintegration of tablet[min]	75	80	105

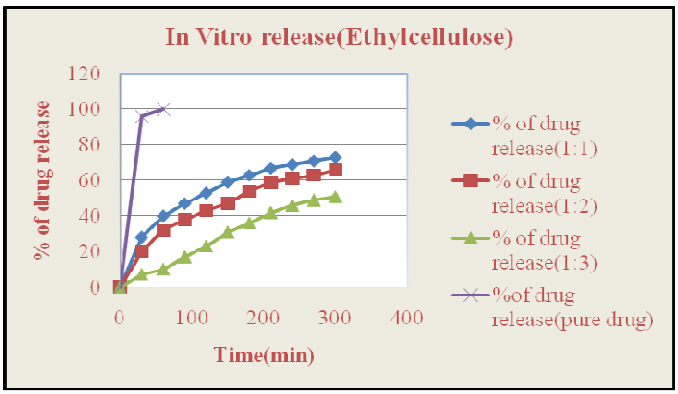
Graphs for In-vitro release



Graph 1: In-vitro release of ISH microencapsulated with PEG 6000 polymer



Graph 2: In-vitro release of ISH microencapsulated with PEG 4000 polymer



Graph 3: In-vitro release of ISH microencapsulated with Ethyl cellulose polymer

Scherrer Equation

XRD Crystalline Size was calculated using Scherrer Formula

$$D_p = \frac{0.94\lambda}{\beta_{1/2}\cos\theta}$$

D_p = Particle size in nanometers

λ = Source wavelength in Angstroms=1.542^{0}A

$\beta_{1/2}$ = Peak FWHM in degrees

2Θ = Peak Position in degrees

Particle size for pure drug of Isoxsuprine HCl [from XRD graph]

$\beta_{1/2}$ =0.46430degrees.

2Θ =25.5713degrees.

$\beta_{1/2}$, 2Θ were substituted in the Scherrer equation

Then,

D_p = 18.3417nm.

Particle size for polymer PEG 6000 & Isoxsuprine HC1 [from XRD graph]

$\beta_{1/2}$ =0.18070degrees.

2Θ =23.0537degrees.

$\beta_{1/2}$, 2Θ were substituted in the Scherrer equation

Then,

D_p = 46.90568nm.

The thickness of the coat with PEG6000 polymer

[Particle size of PEG6000 & ISH – Particle size of ISH] =14.28199nm.

DISCUSSIONS

Disintegration Time

The disintegration time for formulation T-ISH 1:3 with Ethyl Cellulose as the coat material is 105 minutes which is more compared to other formulations. This is suitable for Sustained Release.

The disintegration time for formulations with core to coat material as 1:1 is about an hour which is suitable for conventional tablets.

Amount of Drug released (Dissolution Time)

The drug release pattern for formulation T-ISH 1:3 with Ethyl Cellulose as the coat material is slow and gradual, hence suitable for preparing sustained release tablets.

The formulations with core to coat material as 1:1 are having maximum drug release, hence suitable for conventional tablets.

Mathematical Model Fitting for Drug Release Data

To know the mechanism of drug release of these formulations, the data was fitted into the first-order equation [log cumulative percentage of drug remaining Vs time], Higuchi's equation [cumulative percentage of drug released Vs square root of time] and Korsmeyer et al's equation [log cumulative percentage of drug released Vs square root of time].

First-order equation, Log C=Log C_0 – Kt/2.303.

Higuchi's equation, Q = Kt $^{1/2}$

Koresmeyer et al's equation, M_t/M_∞ = Kt_n

M_t/M_∞ = the fractional solute release

The kinetic data of the drug release for all the three equations are shown in Table-4. When the data was plotted as per the first-order equation, the formulations showed a fair linearity with regression values between 0.9298 and 0.9937[R_1^2].

Table 4: Kinetic values of formulations[8]

Tablet	First order	Higuchi plots	Koresmeyer et al plots	
	R_1^2	R_2^2	Slope(n)	R_3^2
F-I	0.9811	0.9954	0.5032	0.9921
F-II	0.9726	0.9959	0.5876	0.9848
F-III	0.9797	0.9928	0.4435	0.9938
F-IV	0.9876	0.9934	0.5386	0.9957
F-V	0.9922	0.9765	0.5308	0.9678
F-VI	0.9937	0.9629	0.5835	0.9864
F-VII	0.9827	0.9921	0.6190	0.9902
F-VIII	0.9438	0.9932	0.5766	0.9976
F-IX	0.9298	0.9658	0.7180	0.9985

F-I, F-II, F-III---

Isoxsuprine Hydrochloride with PEG 6000 polymer [1:1, 1:2, 1:3].

F-IV, F-V, F-VI---

Isoxsuprine Hydrochloride with PEG 4000 polymer [1:1, 1:2, 1:3].

F-VII, F-VIII, F-IX---

Isoxsuprine Hydrochloride with Ehylcellulose polymer [1:1, 1:2, 1:3].

As the gradient varies, the drug releases and the distance for diffusion increases. This could explain the reason for the drug diffusion at a comparatively slow rate with time. This was referred as the square-root of time of Higuchi's kinetics.

The experiments confirm that the in-vitro release profiles of drug from all the formulations can be best expressed by Higuchi's equation, as the plots showed high linearity [R_2^2: 0.9629 to 0.9959].

To confirm the diffusion mechanism, the data was fitted in Korsmeyer et al's equation. The formulations of all polymers showed good linearity [R_3^2: 0.9848 to 0.9985], with slope[n] values ranging from 0.4435 to 0.6190, indicating that diffusion was the dominant mechanism of drug release for these formulations.

When plotted according to Korsmeyer et al's equation, formulation F-IX showed linearity

[R_3^2 : 0.9985], with a comparatively high slope[n] of 0.7180, which indicates a combination of diffusion and erosion mechanism.

CONCLUSIONS

The granules were white, free flowing and spherical in shape. Physical appearance, hardness, friability, weight variation and uniformity of drug content of different tablet formulations were found to be satisfactory. The tablet hardness varied from 4.0-6.0 kg/cm^2 and friability was less than 0.8%. Uniformity of weight, hardness, friability and percentage of medicament followed the pharmacopeia norms. The prepared tablets showed low weight variations and a high degree of uniformity in drug content. This was mainly due to uniform coating or the spherical nature of the microcapsules leading to proper flow and uniform mixing. The percent of Isoxsuprine Hydrochloride was found to show sustained release when coated with Ethyl cellulose than other coating materials like PEG 6000 and PEG 4000. However, in all the three cases formulation of 1:1 showed maximum drug release. The experiments confirm that in-vitro release profiles of drug from all the formulations could be best expressed by Higuchi's equation as the plot showed high linearity.

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NOMENCLATURE

P^H	Potential of hydrogen
^{0}A	Angstroms
λ	Wavelength
XRD	X-Ray Diffractometer
^{0}c	Degree centigrade
ml	Milliliter
mg	Milligram
ISH	Isoxsuprine Hydrochloride
EC	Ethylcellulose
PEG4000	Polyethylene Glycol4000
PEG6000	Polyethylene Glycol6000
FWHM	Full width at half maximum

T-ISH [1:1], T-ISH [1:2], T-ISH [1:3] --- Tablet of Isoxsuprine Hydrochloride using the polymer in different ratios.