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Investigations on Mucuna Gum as a Drug Release Encapsulate

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ABSTRACT

Drug release retarding polymers are the key performers in sustained release drug delivery system for which various natural, semi-synthetic and synthetic polymers have been investigated. The use of natural polymers over synthetic has gained importance due to their biodegradable, biocompatible, cost effectiveness and safety considerations. The present study deals with isolation of mucuna gum from the species of *Mucuna flagillepes* (*Papillionaceae*) and evaluating its suitability as a microencapsulating agent for delivery of propranolol hydrochloride. The gum was extracted from mucuna seeds by using 1% sodium-meta bisulphite as solvent followed by precipitation with acetone. The extracted gum was evaluated for physical characteristics like melting point, solubility, p^H, total ash and micromeritic properties. Propranolol hydrochloride, a non selective beta-adrenergic receptor blocking agent was chosen as a model drug for formulation of microspheres with different drug**:** polymer [1**:**1-2.5] ratios by emulsification solvent evaporation method. The microspheres were evaluated for yield, particle size, drug loading efficiency and *in-vitro* drug release studies. The drug-polymer compatibility was confirmed by IR spectroscopy. The yield of formulations was found to be between 79 to 90.3% with the average particle size between 55.8 to 74.5µm.The drug encapsulation efficiency of microspheres was found to be in the range of 67.7 to 89.9%. The *in-vitro* drug release studies revealed that the polymer had positive effect on the drug retarding efficiency. The selected microspheres showed sustained and complete drug release up to 12 hours. Thus mucuna gum as a natural biodegradable polymer proved to be a suitable drug release encapsulate.

Keywords: Mucuna gum, Propranolol Hydrochloride, sustained release.

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INTRODUCTION

Oral controlled drug delivery systems represent the most popular form of controlled drug delivery systems for obvious advantages of oral route of drug administration. There are various approaches in delivering a therapeutic substance to the target site in a sustained or controlled release fashion. One of such approach is using microspheres as carriers for drugs[1]. Microspheres are made of polymeric, waxy or other protective materials, synthetic polymers and modified natural products such as starches, gums, proteins, fats and waxes[2]. The use of natural polymers over synthetic is gaining importance due to their biodegradable, biocompatible, cost effectiveness, local availability, low cost, environmental friendly processing methods and safety considerations. Gums are considered to be pathological products formed following injury to the plant or owing to unfavourable conditions, such as drought, by a breakdown of cell walls (extra cellular formation; gummosis) Gums obtained from different sources and their derivatives represent a group of polymers widely used in pharmaceutical dosage forms[3].The polymer for the present investigation (mucuna gum) is a biodegradable polymer extracted from the seeds of the plant *Mucuna flagillepes* (*Papillionaceae*). It is amorphous in nature and insoluble in alcohol. Mucuna seeds contains D-galactose as the major monosaccharide with the presence of D-mannose and D-glucose and has been evaluated for use as a food additive[4].Propranolol, a non selective beta-adrenergic receptor blocking agent was chosen as model drug for formulation of microspheres. It has a short half life of 2-3 hours and undergoes extensive first pass metabolism which raises the need for its sustained delivery[5].

MATERIALS AND METHODS

Materials

Propranolol hydrochloride was procured from Yarrow chem. Products, Mumbai, India. Mucuna seeds were purchased from local market , Bangalore, India. Laboratory reagent grade acetone, petroleum ether were procured from Rankem (RFCL) Limited, New Delhi, India. Sodium metabisulphate was procured from Merck Limited, Mumbai, India.

Methods

Extraction of mucuna gum[6]

Mucuna seeds were roasted at 70 °C for 10 minutes to make the shell brittle. The seeds were dehusked and then autoclaved in a 1% (*m*/*V*) solution of sodium metabisulphite at 121 °C for 15 minutes to inactivate the enzymes and reduce darkening of seeds. Then the seeds were air-dried, pulverized in a blender and the flour obtained was soaked in a solution of 1% (*m*/*V*) sodium

metabisulphite for 24 hours and thereafter passed through a muslin cloth.The resultant filtrate was desolvated with acetone. The product of desolvation (mucuna gum) was dried in a hot air oven at 35^{O}C for 4hours, powdered, passed through sieve #60 and stored in desiccator.

Preparation of mucuna gum microspheres of propranolol hydrochloride

The microspheres were prepared by emulsification solvent evaporation method with drug to polymer concentration varied in ratios of 1:1, 1:1.5, 1:2, and 1:2.5 (Table 3). Arachis oil was heated at 70^{O}C and the aqueous phase consisting of polymer (mucuna gum) and drug was added to form an emulsion maintaining the constant stirring rate of 1000rpm. Constant volume of acetone was added and stirring continued for 1 hour. The formed microspheres were filtered, washed with petroleum ether until the oil was removed and dried at room temperature.

EVALUATION METHODS

Phytochemical Examination[7]

Preliminary tests were conducted to confirm the phytochemical constituents obtained. The test for presence of gums (Ruthenium Red), carbohydrates (Molisch's test, Fehling's test), alkaloids (Mayer's test and Dragandroff's test) and proteins (Millon's test) were performed.

Physicochemical Properties[8]

Solubility studies

The solubility study of extracted mucuna gum was performed in water, acetone, methanol, chloroform, petroleum ether, dichloromethane.

Melting Point

The dried, powdered mucuna gum was sealed in capillary tubes and melting point was determined in Tehsil's tube containing liquid paraffin. Slowly temperature was raised and the temperature at which it undergoes colour change was recorded.

pH determination

The mucuna gum solution of 1%w/v was prepared in water and pH was measured using a digital pH meter (ELICO LI 613).

Bulk density

A weighed quantity of the mucuna gum was passed into a graduated measuring cylinder. The mucuna gum powder was carefully leveled in the cylinder without compacting. The unsettled apparent volume was read to the nearest graduated unit and noted.

The bulk density was calculated by using the formula,

$$\text{Bulk density} = \frac{\text{Weight of the powder blend}}{\text{Bulk volume}}$$

Tapped density

It is determined by using tapped density apparatus and the change in the volume of powder sample after tapping is noted. It is calculated using the following equation,

$$\text{Tapped density} = \frac{\text{Weight of the powder blend}}{\text{Tapped volume}}$$

Loss on drying

A weighed quantity of mucuna gum was taken in a petriplate and placed in a hot air oven maintained at 105^{O}C for 1 hour. The petriplate was removed and reweighed and loss on drying was calculated using the formula

$$\text{Loss on drying} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

Total ash value[8]

A weighed quantity of mucuna gum was placed in a silica crucible and incinerated at a temperature not exceeding 450^{o}C until free from carbon, cooled and weighed. The percentage was calculated based on dried substance basis.

Drug – Polymer compatibility study[9]

Drug (propranolol hydrochloride) - polymer(mucuna gum) compatibility was studied by IR spectral studies. The IR spectrum of drug, polymer and physical mixture of drug and polymer in 1:1 ratio were recorded using FT-IR spectrophotometer (FTIR 8400 S, Shimadzu, Japan).

The drug, polymer samples were triturated with finely powdered and dried potassium bromide. The mixture was then placed in sample cell and spectra were recorded by scanning it over the range of 4000-400cm^{-1}.

Evaluation of mucuna gum microspheres

Yield of microspheres[9]

The percentage yield of microspheres was calculated by the following formula

$$\% \text{ yield} = \frac{\text{Actual weight of product}}{\text{Total weight of drug and excipient}} \times 100$$

Particle size analysis[9]

Particle size analysis was performed by using OLYMPUS trinocular optical microscope with 40X optical zoom and photographs were taken for all formulations. The average of the particle size was calculated by using Microlite image software.

Drug content[10]

Microspheres equivalent to 100mg of propranolol hydrochloride was weighed and extracted by sonicating with 0.1N hydrochloric acid and filtered. The filtrate was further diluted and the drug

content was estimated for the drug content at 289nm using UV-Spectrophotometer (UV 1601-Shimadzu, Japan).

Entrapment efficiency

The drug entrapment efficiency of all the microsphere formulations was calculated by using the equation:

$$\% \text{ Drug entrapped } = \frac{\text{practical percent drug content}}{\text{theoretical drug content}} \times 100$$

***In-vitro* drug release** [11,12]

The release of propranolol hydrochloride from the mucuna gum microspheres of different formulations was studied in 0.1N hydrochloric acid (1000ml) using USP XXIII basket Dissolution test apparatus (Labindia DS 8000) with stirring speed of 100 rpm and temperature 37 ± 0.5°C. Sample of microspheres equivalent to 100 mg of propranolol hydrochloride were weighed and loaded into empty hard gelatin capsule shells and used for the test. Samples were withdrawn at one hour interval and estimated for drug content at 289 nm using Shimadzu UV-1601 UV Double beam spectrophotometer. The drug release of the formulations was compared with the pure drug propranolol hydrochloride.

***In-vitro* drug release kinetics**

Data obtained from *in-vitro* drug release studies were fitted to various kinetic models like zero-order, First order, Higuchi, Korsemeyer and Peppas using PCP Disso V3 to predict the drug release kinetics.

RESULTS AND DISCUSSION

The method for the isolation of mucuna gum from the seeds of *Mucuna flagillepes* was stabilized with a practical yield of 15% .

The preliminary phytochemical examination of the gum confirmed the presence of carbohydrates, absence of alkaloids, proteins and obtained substance was confirmed to be mucuna gum (Table 1).The physicochemical properties of the extracted gum summarised in (Table 2) elicited that the polymer was soluble in water and insoluble in organic solvents. The melting point of the gum was as high as about 190-200^{0}C with total ash content of 6%w/w with the LOD of 0.33%

The IR spectra of pure drug, polymer and physical mixture indicated the absence of any possible drug-polymer interaction as indicated in Figure 1.

The microspheres formulations of propranolol using mucuna gum as drug encapsulate was established by emulsification solvent evaporation method. The average particle size of all

formulations ranged between 55.86 to 74.5µm (Figure 2). As the concentration of mucuna gum was increased, the microspheres showed rough and rugged edges with increase in particle size.

Table 1: Phytochemical Tests for extracted mucuna gum

Sl.No.	Identification	Name of the test	Observations
1.	Tests for carbohydrates	Molisch's test, Fehling's test	Positive test confirms the presence of carbohydrates.
2.	Test for alkaloid	Mayer's test and Dragandroff's test	Negative test indicates absence of alkolids.
3.	Test for proteins	Millon's test	Negative test indicates absence of proteins.

Table: 2 Evaluation properties of mucuna gum

Evaluation property	Results
Solubility	Soluble in water, practically insoluble in acetone, methanol, chloroform, petroleum ether, dichloromethane
Melting Point	190-200°C
P^H of 1% Solution	Between 6-7
Bulk Density	0.32g/ml
Tapped density	0.48g/ml
Carr' s index	33.3%
Total ash	6%w/w
Loss on drying	0.33%

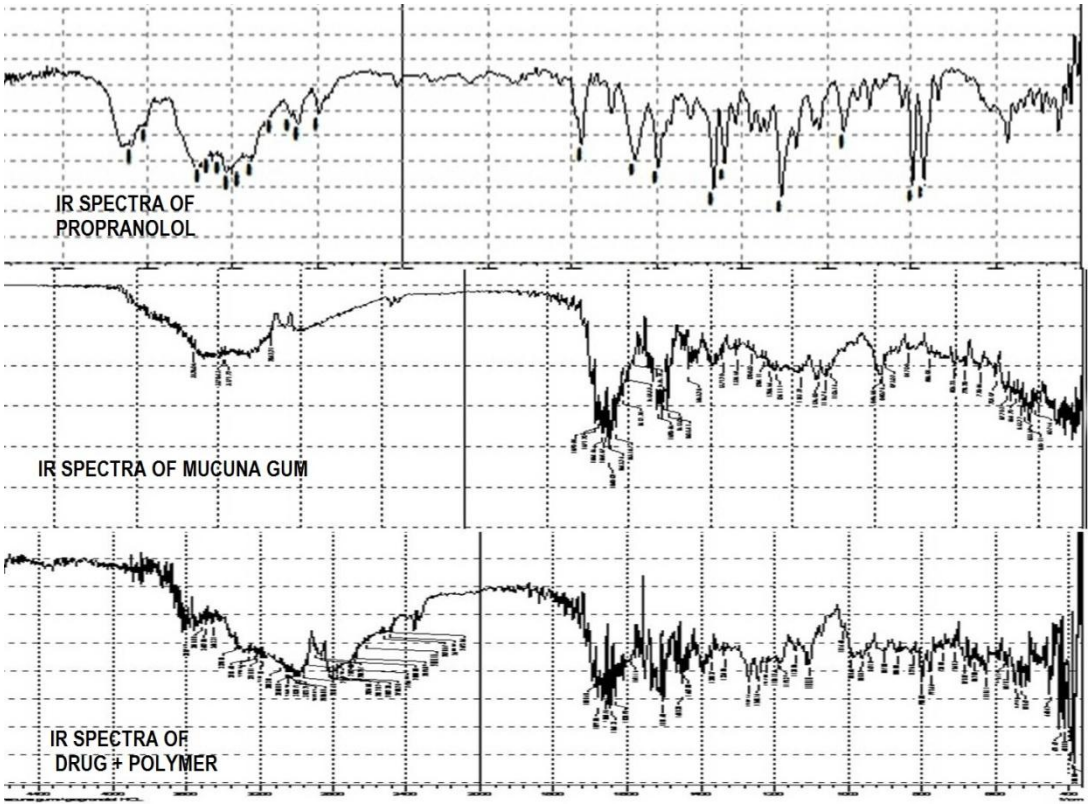

Figure 1: IR spectra of Propranolol hydrochloride, Mucuna gum and Drug: Polymer

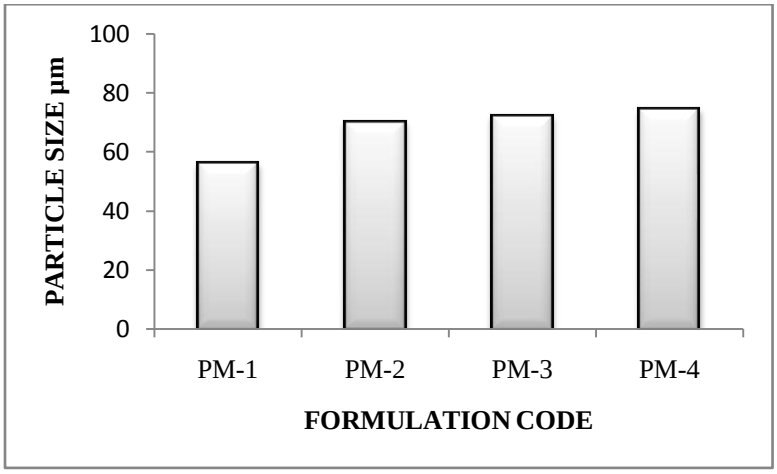

Figure 2: Comparative particle size distribution profile of all the formulations

The results of all evaluation parameters are indicated in Table 4. The yield of all the formulated microspheres was found to be in the range between 79.0 to 90.3%. The drug entrapment efficiency of all formulations was found to be 67.7- 89.9%.

Table 3: Formulation of mucuna gum microsphers

Sl. no	Ingredients	PM-1 Drug : Polymer(1:1)	PM-1.5 Drug : Polymer(1:1.5)	PM-2 Drug : Polymer(1:2)	PM-2.5 Drug : Polymer(1:2.5)
1.	Propranolol Hydrochloride	500mg	500mg	500mg	500mg
2.	Mucuna gum	500mg	750mg	1000mg	1250mg
3.	Arachis oil	100ml	100ml	100ml	100ml
4.	Acetone	20ml	20ml	20ml	20ml

Table 4 : Evaluation of mucuna gum microspheres

Formulation code	Formulations drug: polymer	% yield	% content	Drug entrapment %
PM-1	1:1	79.0	95	67.7
PM-1.5	1:1.5	88.2	92.5	80.4
PM-2	1:2	90.3	82.5	89.9
PM-2.5	1:2.5	82.8	81	74.7

The *in-vitro* drug release profile of all the formulations are indicated in the Figure 3. The studies revealed that the formulation PM-2.5 containing maximum concentration of mucuna gum showed a slow and sustained release up to 12 hours. The results also indicated that as the concentration of mucuna gum was increased the drug release rate was retarded.

The *in-vitro* drug release data was studied for best fit model and the results of highest r^2 value (Table 5) proved that all the formulations exhibited matrix type as the drug release kinetics model.

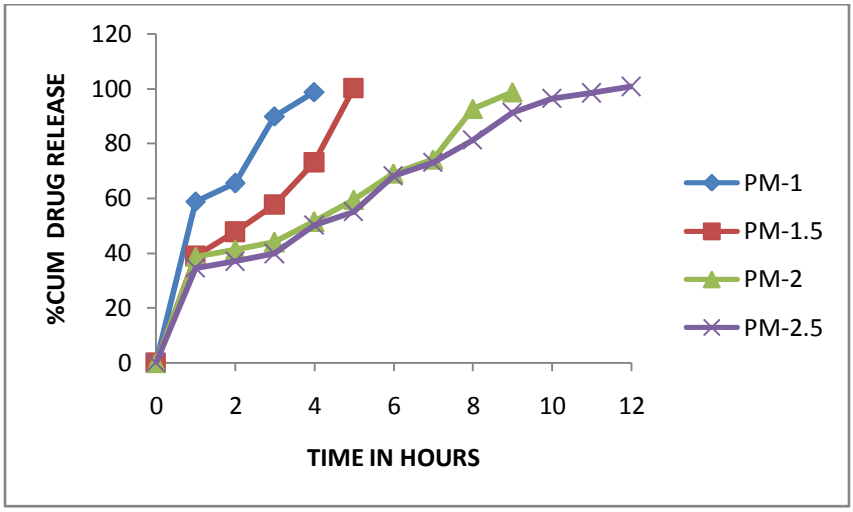

Figure 3: Comparative *in-vitro* drug release profile of microsphere formulations

Table 5: *In-vitro* drug release kinetics data

Formulation code	Zero order		First order		Matrix		Hix. crow		Korsmeyer peppas Equation		
	r^2	k	r^2	k	r^2	k	r^2	k	r^2	n	k
PM-1	0.863	29.08	0.851	-1.316	0.989	51.75	0.970	-0.206	0.970	0.345	60.267
PM-1.5	0.940	19.66	0.8761	-0.463	0.979	37.99	0.939	-0.108	0.955	0.499	37.520
PM-2	0.879	11.79	0.8592	-0.301	0.971	30.15	0.933	-0.067	0.920	0.402	35.020
PM-2.5	0.903	9.677	0.8138	-0.329	0.987	28.31	0.962	-0.061	0.961	0.472	29.461

CONCULSION

A naturally occurring biodegradable mucuna gum polymer was isolated and its suitability as an encapsulating agent was studied. The microspheres of propranolol hydrochloride with sustained release upto 12 hours could be achieved. Thus mucuna gum was found to be a suitable drug encapsulating agent.

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