RESEARCH PAPER

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Controlled Release Pellets of Isoxsuprine Hydrochloride

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A multiparticulate controlled release formulation of Isoxsuprine HCl was developed which comprised of spherical pellets coated with a rate controlling membrane. The pellets were prepared using Extrusion-Spheronization technology. Studies were undertaken to design a prototype formula for the drug cores which is amenable to spheronization. The pellets were coated using nonaqueous solutions of polmers such as ethyl cellulose and Eudragits by pan coating technique. The successful formulations were then evaluated for their pellet characteristics, *in vitro* release profiles and stability.

MULTIPARTICULATE systems offer some advantages over single unit preparations. The gastric emptying occurs gradually in a more consistent manner with small individual variations[1]. They yield more predictable drug release profile and there is a better statistical assurance of drug release[2,3]. The risk of dose dumping is equally subdivided due to the individual units releasing the drug[4].

The objective of the present investigation was to develop a multiple unit controlled release system of Isoxsuprine HCl, a vasodilator and uterine relaxant. The drug has a biological half life of 1.5 hours and the oral dose is 10-20 mg four times a day[5]. Since it is an adrenergic drug, slight increase in plasma levels of the drug may cause tachycardia and hpotension. The narrow therapeutic index of the drug makes it suitable for administration in the form of multiple unit dosage form which has an assurance against risks of dose dumping.

Extrusion-Spheronization is widely used method for pelletization which involves extrusion of wet mix of drug and excipients into short rods followed by rounding of the rods into spherical cores on a spheronizer plate[6]. The effect of excipient variables and process variables on the final product characteristics has been widely studied[7].

Coating of the pellets with a non-soluble barrier membrane offers a reliable method of regulating the drug release from the pellets[8]. The coat can be varied in nature and thickness to give the desired release profile. Spherical pellets posses ideal shape for application of the coat. The paper describes development and **in vitro** evaluation of a multiparticulate controlled release preparation of Isoxsuprine HCl.

EXPERIMENTAL

Materials

Isoxsuprine HCl I.P. Avicel PH Iol, Avicel RC-581, Lactose I.P., Dicalcium Phosphate I.P. (DCP), Talc I.P. Starch I.P., Hydroxypropyl methyl cellulose USP (HPMC), Polyvinyl Pyrrolidone (BDH) (PVP), Ethyl Cellulose (BDH) (14cps), Eudragit RS, Eudragit RL (Rohmpharma), Dibutyl Phthalate (DBP), Diethyl phthalate (DEP), sodium CMC I.P.

All other materials, solvents and reagents used were of analtical grade.

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METHODS

a) Fabrication of drug cores

Avicel PH 101 and lactose in combination (1:1) was used as the filler base. The dose of the drug selected was 40 mg. Drug and matrix materials were sieved through 80 mesh screen, weighed and mixed. The mixture was kneaded using water as the binder which was then extruded through 22 mesh screen and spheronized on a marumerizer (Fuji Paudal, Japan) fitted with 1 mm cross hatch pattern friction plate at a speed of 1100 rpm and a dwell time of 3 minutes. The pellets obtained were dried on paper lined trays in a hot air oven at 50°C for 2 hours.

For standardisation of the pellet formulations pellets were prepared by hand extrusion (batch size 10 gms). The prototpe was subjected to excipient variables like filler type, filler concentration, moisture content of the mix, binder type and lubricants; and process variables like extruder screen size, spheronization time and spheronizer speed. The pellets obtained were evaluated for percent yield, mean particle size, sphericity and drug release profile. Based on these characteristics the best prototype was selected.

b) Scale up studies

The formulation was investigated for successful scale up with respect to independent variables. The batch size was increased to 250 gms and the extrusion was carried out on Fuji-Paudal EX-DS 60 extruder.

c) Coating of pellets

The pellets obtained were coated with water insoluble polymers to confer upon them slow release properties. The coating was carried out in a coating pan equipped with hot air supply. The cores were warmed to a bed temperature of 37°C. The polymer solutions were then applied by intermittent air borne spray using a pilot spray gun at a pressure of about 20 psi and a rate of 1ml/min for a load of about 75 gms of drug cores, A 5-10 seconds spray on and spray off cycle was followed taking care that the drug cores did not become tacky. After application of the required amount of the solution, determined on coat weight basis, the pellets were allowed to roll with warm air at 40-45°C for 10 minutes. Different spray compositions and amounts of applications are summarized in **Table-1.**

d) Evaluation of the pellets

1) **In Vitro release profile:** The coated pellets were evaluated for **in vitro** release profile using Type II USP XXI dissolution apparatus by change of buffer method wherein the medium consisted of buffer of pH 1.2 for first hour, pH 4.5 for the next hour and pH 7.2 for the rest of the period. The medium was maintained at 37°C and the peddle was operated at 100 rpm. 5 ml of aliquots were withdrawn at hourly intervals and replaced by fresh dissolution medium. The drug released was determined spectrophotometrically at 268 nm on a Bausch and Lomb Spectronic 2000 spectrophotometer.

2) **Drug Content:** The pellets were extracted in methanol. The resulting solution was evaporated and the residue was dissolved in glacial acetic acid. This was then titrated against 0.1 N Perchloric acid potentiometrically using Mettler DL 40 GP memotitrator.

   The pellets were also evaluated for percent friability, density, porosity, flow properties, surface area and sphericity. Sphericity was determined using ratio of length and width of the pellets[9].

3) **Stability Studies:** The pellets were subjected to accelerated stability studies by storing them at 37°C ± 1°C, 45°C ± 1°C, 60°C ± 1°C and 85% R.H. at 37°C for a period of 3 months and at room temperature for a period of one year. The samples were evaluated for appearance, drug con-

Table 1: Spray compositions of different polymers

Polymer	Solvent system	Polymer concentration(%)	Coat weight applied (%)
Sodium CMC	Alcohol-Water (1:1)	1	0.8
			2.0
			2.4
Ethyl Cellulose	Isoprapanol Methylene chloride (1:1)	2.5	0.5
			1.36
			3.94
		5	1.6
			3.56
			5.03
Eudragit RS	Acetone Isopropanol (1:1)	5	3.2
			9.8
			14.4
			5.25
		10	15.25
			19.11
Eudragit RL	Acetone Isopropanol (1:1)	5	10.32
			12.82
			15.36

tent and **in vitro** release profiles at regular intervals.

RESULTS AND DISCUSSION

A) Fabrication of drug cores

It was found that Avicel-lactose combination in a ratio 1:1 formed very good pellets with smooth surface characteristics and was therefore used as the filler base for Isoxsuprine HCl pellets. Since the dose of the drug was as low as 40 mg, 90% of the filler base could be used to form pellets of 99.87% sphericity. A moisture content of 42.85% was found to be optimum with a percent yield of 89.91 % in the desired size range of 0.8 - 1 mm. It was found that when lactose was replaced by DCP, sphericity was drastically reduced to 90.18% and surface roughening was observed. When Avicel RC-581 was included in the filler base, excellent spheroids with 98.95% sphericity were obtained.

Water was found to have good binding properties but replacement with 2% PVP solution or 1% HPMC solution resulted in pellets with good mechanical strength. Lubricants when added at any stage of pelletization had no added advantage on pellet characteristics.

Extruder Screen of 22 mesh was found to yield pellets with the desired mean particle size. A spheronization speed of 690 rpm yielded 89.28% of pellets on the desired size range with a sphericity of 98.31%. However, a variable speed i.e. gradual increase of speed over time was found to be the best processing condition. A spheronization time of

Table-2: Pellet Characteristics

Parameter	Value
1. Mean percent drug content (%) ± S.D.	99.12 ± 2.15
2. Percent friability (%)	0.018
3. Mean particle size (mm)	0.908
4. Surface area (mm^2)	2.711
5. Sphericity(%)	99.89
6. True density (g/ml)	1.544
7. Bulk density (g/ml)	
a. Aerated	0.769
b. Tapped	0.833
8. Angle of Repose (°)	26.565
9. Flow rate (g/sec)	16.25

3 minutes was required to get the desired pellet characteristics.

Thus Isoxsuprine HCl pellets were fabricated using Avicel-lactose (1:1) combination as filler base with a drug-diluent ratio of 10:90 using 2% PVP solution as the binder by extrusion through a screen size of 22 mesh and spheronizing at a variable speed [570 rpm (1min) 830 rpm (1min) and 1100 rpm (1min)] for 3 minutes on the spheronizer plate.

Scale up studies showed that the moisture content required for satisfactory spheronization reduced to 41.6% as the batch size increased. Similarly spheronization time was increased to 5 mins due to increased spheronizer load.

The pellets obtained exhibited satisfactory pellet characteristics as shown in **Table 2**. Evaluation of the pellets for drug release profile revealed that the drug was released within 45 minutes. Hence application of a barrier coat was required to retard the release which was achieved by pan coating.

B) Coating of the pellets

Of all the polymers tried, ethyl cellulose and Eudragit Rs 100 used in the form of non aqueous solutions could be successfully employed as release retar dants for Isoxsuprine HCl pellets. Sodium CMC when used in the form of 1% hydroalcoholic solution, plasticized with 25% w/w of DBP was able to retard the release of the drug at a coat weight of 2% wherin 99% of the drug was released within 9 hours. However, further increase in the coat weight did not further retard the release, 5% w/v solution of ethyl cellulose, plasticized with 20% w/w of DBP at a coat weight of 5.3% was found to satisfactorily retard the release of the drug. First order release profile with t_{50} value of 3.8 hours was obtained (**Fig. 1**) 5% w/v solution of Eudragit RS plasticized with 10% w/w of DEP at a coat weight at 14.42% could also effectively retard the drug release. Zero order release with t_{50} value of 4.4 hours was obtained (Fig. 1).

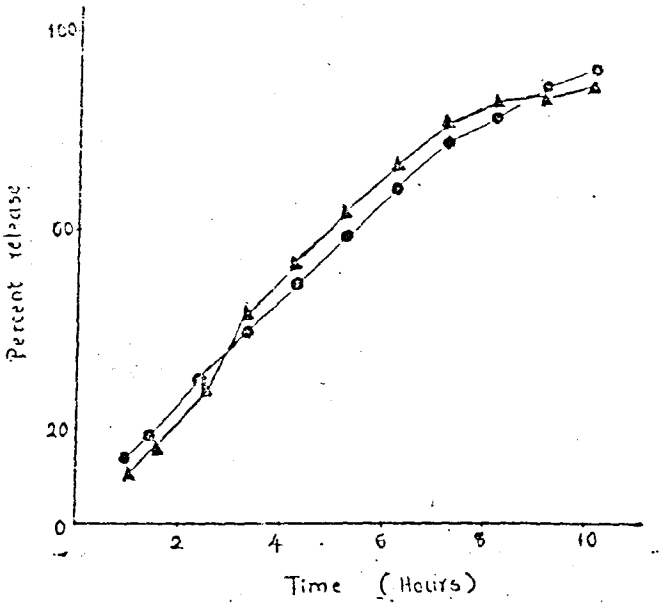

Fig.1: Release profiles of Isoxsuprine HCl coated pellets.
Key Δ– Δ Ethyl cellulose coated
O - O Eudragit coated

C) Stability studies

Accelerated stability studies revealed that both the formulations coated with ethyl cellulose as well as Eudragit RS showed no change in release profiles at all the conditions except at 60°C. Room temperature stability studies however showed that both the formulations were stable for a period of one year with respect to appearance, drug content and drug release profile.

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