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SPRAY DRIED INDAPAMIDE MICROPARTICLES FOR CONTROLLED RELEASE – A NOVEL APPROACH

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ABSTRACT

The aim of the present study was to prepare and evaluate microparticles of Indapamide using blend of HPMC and Ethyl Cellulose by Spray drying technique for controlled release. Sieve analysis data indicated that the prepared microparticles were in the ranges of 265 µm to 187µm. The angle of repose, % Carr's index and tapped density were well within the limit, indicating reasonable good flow potential for the prepared microparticles. SEM photographs and calculated sphericity factor confirms the prepared formulations are spherical in nature. DSC studies and FT-IR spectra showed that the encapsulated drug was stable in the prepared formulations. The prepared formulations were analyzed quantitatively for the amount of encapsulated drug. From the drug loading, encapsulation efficiency and *in vitro* drug release data, F6 was selected as optimized formulation. The optimum formulation F6 shows the drug release of 90.56 % up to 24 h and having drug loading and encapsulation efficiency of 66.82 ±0.27 % and 96.36 ±0.19 % respectively. It was also observed that, there was no significant release of drug at gastric pH. The release kinetics for all the formulations indicated that drug release followed non-Fickian diffusion. The optimized formulation was subjected for stability studies.

KEY WORDS

Indapamide, Microparticles, Controlled release, Spray drying technique.

INTRODUCTION

Indapamide is an oral antihypertensive/diuretic, indicated for the treatment of hypertension. Indapamide is thought to exert its antihypertensive effect by its diuretic action; several investigations employing laboratory animal preparations have documented a direct vascular action. It has been categorized as a calcium channel blocking agent and this may account for a portion of its antihypertensive effectiveness. In both the treatment of edema and as an antihypertensive agent, indapamide appears to be comparable to hydrochlorothiazide, chlorthalidone and furosemide and seems to have no clinically important advantage over these agents. Side effects associated with indapamide are minimal and appear to be comparable to those observed with other antihypertensive diuretics. Based on few published studies, indapamide appears to be a useful long acting antihypertensive and diuretic agent that is well tolerated and associated with minimal biochemical abnormalities or side effects.

The research work aims to develop a formulation that can deliver indapamide for extended periods of time for once a day administration. This may offer significant

patient benefits by reducing the number of daily doses compared to conventional therapies[1].

MATERIALS AND METHODS

Preparation of microparticles [2-6]

Required amount of ethyl cellulose and HPMC K4M were dissolved in 1:1 ratio of dichloromethane and ethanol (96%). To this solution, required amount of indapamide was added to obtain the following drug: polymer ratios viz., 1:8:2, 1:8:4, 1:12:2, 1:12:4, 1:4:2 and 1:4:4. Spray drying was co-currently performed using a LSD-48 mini spray drier (JISL, Mumbai), with a standard 0.5 mm nozzle. In the standard condition, the inlet temperature, spray flow and compressed spray air flow (represented as the volume of the air input) were set at 72°C, 5-6 mL/min, and 10 L/min, respectively. The final solutions were sprayed through 0.5 mm nozzle by a flow of compressed air (air pressure 1.5 kg/cm^2). The solvent evaporation by a flow of heated air aspirated by a pump (29-35 ASP, corresponding to 50-60 mm –ve pressure), induced the formation of solid microparticles from the drop. The obtained particles separated in a cyclone separator and settled into a collector. The collected formulations were stored under vacuum in a dessicator till further analysis.

Table 1
Formulation chart for the prepared indapamide microparticles.

	Ingredients in (mg/ml)		
Formulation No.	**Indapamide**	**Ethyl Cellulose**	**HPMC**
F1	2.5	20	5
F2	2.5	20	10
F3	2.5	30	5
F4	2.5	30	10
F5	2.5	10	5
F6	2.5	10	10
F7	2.5	20	-
F8	2.5	10	-
F9	2.5	-	20

Characterization of microparticles[7-9]

Size distribution

The particle size was measured using Malvern Mastersizer 2000 version 5.1 (Malvern, UK.). The samples of spray dried microparticles were dispersed in 1:20 with methanol and measured at temperature of 37°C.

Scanning Electron Microscopy (SEM) and sphericity

SEM photographs were taken for the prepared microparticles with a scanning

electron microscope, Joel-LV-5600, USA, at the required magnification in room temperature to confirm the morphological characteristics

microparticles was determined by using camera lucida, by taking the tracings of the microspheres on a black paper at a magnification of 45x. The circulatory factor (S) was calculated as

$$S = \frac{P^2}{12.56 \times A}$$

Where 'A' is area (cm^2) and 'P' is the perimeter of the circular tracing.

Fourier Transform Infrared spectroscopy (FT-IR)

The characteristic peaks of pure drug were compared with the peaks obtained with the formulation using KBr pellet.

Differential scanning calorimetry (DSC)

All dynamic DSC studies were carried out on Dupont thermal analyzer with 2010 DSC module. The instrument was calibrated using high purity indium metal as standard. The dynamic scans were taken in nitrogen atmosphere at the heating rate of 10ºC/min.

Estimation of drug loading and encapsulation efficiency

Drug loading and percentage encapsulation efficiency of the prepared microparticles was estimated. 100 mg of microparticles were crushed, dissolved and suitably diluted with methanol and absorbance was measured at 280 nm using UV visible spectrophotometer (Pharmspec 1700, Shimadzu Corporation, Japan).

In vitro drug release studies[10-12]

The *in vitro* release of drug from the microparticles was carried out in basket type dissolution tester USP XXIII, TDT-08L, containing pH 1.2 buffer for first 2 hr and with pH 7.2 phosphate buffer for the next 22 hr. The volume of the dissolution media taken was 900 mL and basket was constantly rotating at 100 rpm, bath temperature was maintained at 37 ± 0.5°C. Aliquots (10 mL) of dissolution media were taken at specified time which was subsequently replenished with equal amount of fresh media and samples are analyzed for drug content. The release data obtained were fitted into various mathematical models to interpret drug release. Dissolution studies were carried out in triplicates for all the batches of the prepared formulations and compared with commercial formulation Lorvas® tablet.

Further, the differential factor (f_1) and similarity factor (f_2) were calculated for the prepared formulations and marketed formulation.

RESULTS AND DISCUSSION

Different parameters like temperature of inlet air, drying temperature, concentration of different polymers and drug, feed rate, inlet air pressure and aspirator speed was optimized during the process. It was done to get the maximum yield of microparticles with minimum loss of drug during spray drying. Optimum drying conditions were employed for the process.

Spherical discrete microparticles were obtained by spraying the drug-polymer solution. The values of this range indicate a powder product with wide size distribution. The optimum drug to polymers ratio of 1:4:4 w/w was used (F6). Particle size analysis data indicated that the prepared microparticles were of particle size range from 7.83 μm to 11.42 μm. The yield of the microparticles was up to 97%.

SEM photographs showed that the spray dried microparticles were spherical in nature with homogeneous characteristics and smooth appearance. They didn't show the presence of free drug on the microparticles surfaces (Fig. 1). These morphological characteristics indicate that the drug is dispersed through the polymeric and spherical nature of microspheres. Sphericity of the prepared

system (microparticles). The sphericity of the prepared microparticles was also calculated and confirmed by camera lucida tracings. The calculated sphericity values were less than 1, confirming the sphericity of the microparticles.

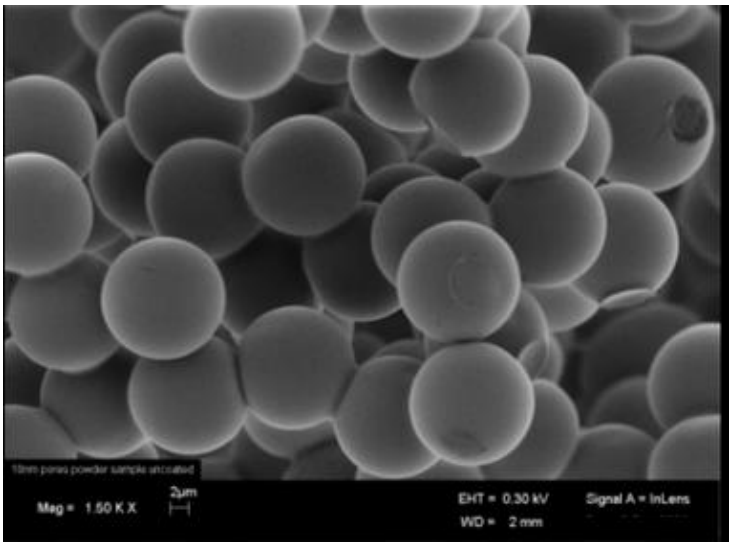

Fig 1

SEM Photograph of Formulation F6

FT-IR spectra showed that the characteristics bands of indapamide were not altered after successful encapsulation without any change in their position, indicating no chemical interactions between the indapamide and excipients used as shown in Fig 2.

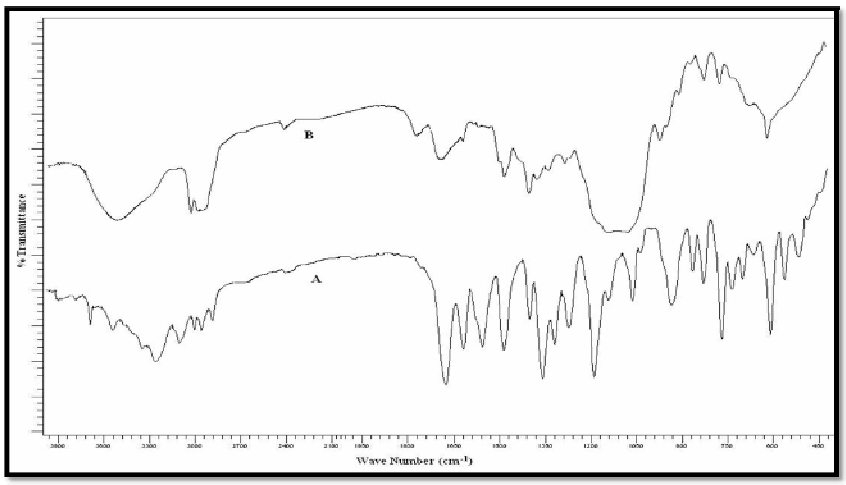

Fig 2

FTIR spectra of Pure drug Indapamide (A) and formulation F6 (B).

DSC studies revealed that indapamide was molecularly dispersed inside of the microparticles. Pure drug exhibited a sharp endothermic peak at 178.25°C. It was observed that

presence of the endothermic peak at 179.06°C in the drug loaded microparticles indicated, that the drug was present in the intact form within the microparticles, in form of a solid solution. Further, no crystalline drug was detected, which augmented that drug is present as molecular dispersion within the microparticles as showing Figure 3.

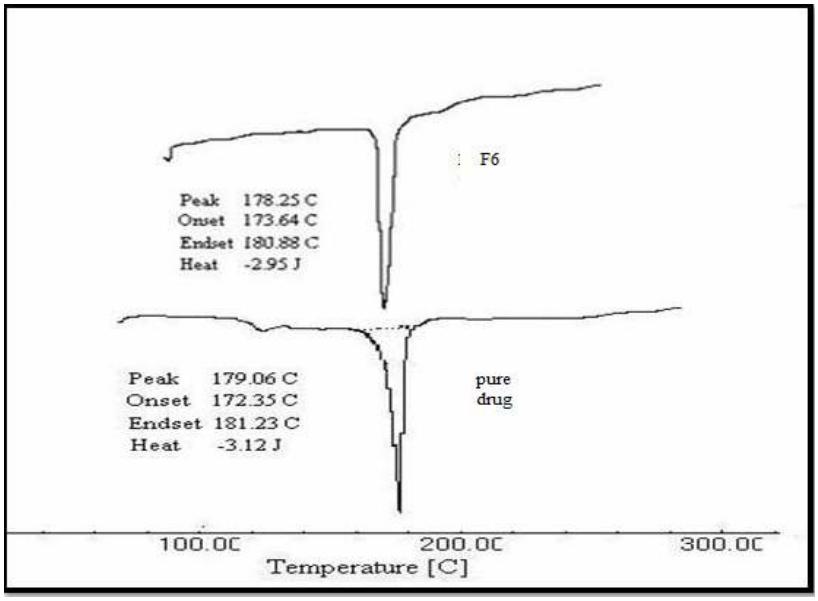

Figure 3
DSC thermogram comparison for Indapamide pure drug and formulation F6

Drug loading and entrapment efficiency increase with increase in the polymer concentration however drug loading and entrapment efficiency also depend on proper ratio of both polymers as shown in table 2. The percent of drug loading in the formulations were in the range of 26.32±0.28 % to 66.82 ±0.27 %.

Table 2
Drug loading and encapsulation efficiency of prepared microparticles

Formulation	*Drug loading(%) mean ± SD**	*Encapsulation efficiency (%) mean ± SD**
F1	46.74±0.23	58.23±0.36
F2	51.26±0,18	65.43±0.25
F3	56.68±0.24	74.80±0.24
F4	59.53±0.21	80.41±0.17
F5	50.38±0.29	51.96±0.21
F6	66.82 ±0.27	96.36 ±0.19
F7	36.84±0.19	43.4±0.27
F8	26.32±0.28	37.5±0.23
F9	29.75±0.25	36.58±0.17

*Standard deviation, n = 3

From the results it can be inferred that there is a proper distribution of indapamide in the microparticles. *In vitro* release studies shows significant amount of drug release was observed at gastric pH from microparticles. Drug release of all prepared formulations was shown in figure 4. In case of optimized formulation (F6) it was found that at the end of 24th hr, amount of drug release from formulation was controlled than any other formulations in the intestinal environment. In vitro release of optimized formulation (F6) was further compared with release data of marketed product Lorvas® tablet as shown in figure 5. It was found that there was no significant difference between release pattern of optimized formulation (F6) and marketed product. Drug release was found to be in similar fashion as that of marketed product thus stating the acceptability of formulation F6.

The values of $t_{50\%}$ enhanced with further increase in ethyl cellulose concentration and decrease in HPMC K4M ratio were observed. These findings indicated considerable release retarding potential of the ethyl cellulose and HPMC K4M blend. The rate of drug release followed first order kinetics and statistically estimated values of 'n' at the 95% confidence limit, the values of 'n' are in the range of 0.32 to 0.42, indicated that the drug release from all microparticles was by fickian diffusion. The obtained values of differential factor (f_1 = 6.35-8.19) and similarity factor (f_2 = 58.26-79.16) suggested that the dissolution profile of the prepared formulations and marketed formulation are similar.

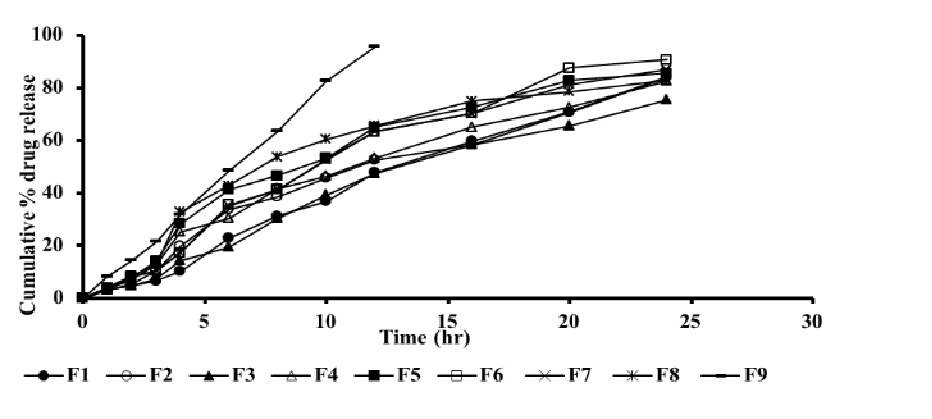

Fig 4
Drug release profile of indapamide from prepared formulations.

F1(-●-), F2(-○-),F3(-▲-),F4(-Δ-),F5(-■-),F6(-□-) , F7(-□-), F8(-*-), F9(-ˉ-)

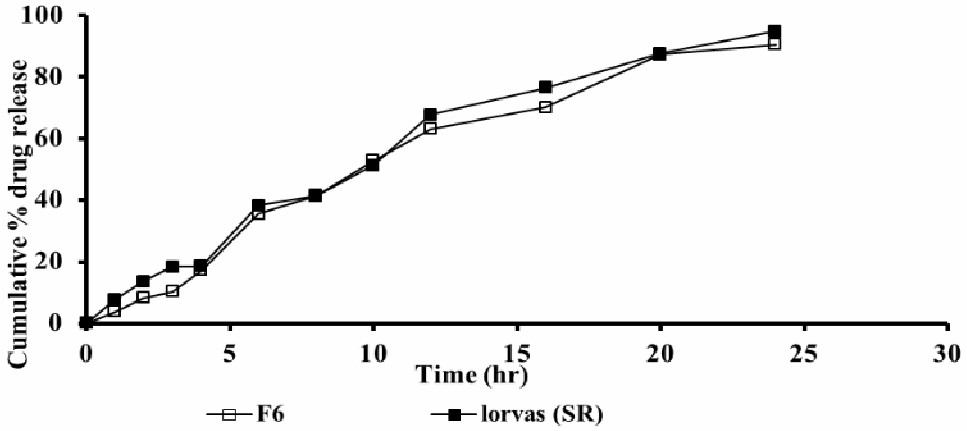

Fig 5
Comparative drug release profile of optimized formulation F6 with marketed product Lorvas® tablet. F6(-□-), F7(-■-)

CONCLUSION

From the present study, it can be concluded that the prepared drug loaded microparticles demonstrate the potential use of ethyl cellulose and HPMC K4M blend for the development of controlled drug delivery systems for highly water soluble drug using spray drying technique. It was found that prepared microparticles from spray drying technique posses good sphericity and prepared microparticles shows similar drug release in same fashion when compared with marketed product. The DSC thermogram obtained for the pure drug and formulation shows no significant shift in the endothermic peaks confirming the stability of the drug in the formulation. From the FT-IR spectra, it was observed that similar characteristic peaks appear with minor differences for the drug and formulation. Hence, it can be concluded that there was no chemical interaction between the drug and the polymer used. Hence it is stated that indapamide could be formulated into microparticles as controlled drug release dosage form.

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