

**PREPARATION AND EVALUATION OF MICROPOROUS DRUG DELIVERY SYSTEM****GOWDA.D.V., KHAN M. S\*, NAWAZ MOHAMMED AND SHIVAKUMAR H.G.**

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**ABSTRACT**

The aim of the present study was to prepare and evaluate microporous pellets loaded with Indapamide (IP) using blend of Avicel PH 101 (Microcrystalline cellulose) and sodium chloride (NaCl) by extrusion/spheronization technique for controlled release. Solid, discrete, reproducible pellets were obtained. Sieve analysis data indicated that the size of prepared pellets were in the range of 1135  $\mu\text{m}$  to 1245 $\mu\text{m}$ . Prepared pellets were spherical in shape, have dent surfaces with pores on the surface, as evidenced by scanning electron microscopy (SEM). The pellets were characterized for micromeritic properties and encapsulation efficiency. Molecular level drug distribution and compatibility of the drug after encapsulation in the pellets were confirmed by differential scanning calorimetry (DSC) and by Fourier-transform infrared (FTIR). The prepared pellets were analyzed quantitatively for the amount of encapsulated drug. Studies such as drug loading, encapsulation efficiency and *in vitro* drug release indicated F3 as optimized formulation. The optimum formulation F3 shows 91.41 % drug release up to 24 h. It was also observed that, there was no significant release of drug in gastric pH. The release kinetics for all the formulations indicated that drug release followed non-Fickian diffusion. The stability studies performed on F3 showed no significant difference in drug content. It was concluded that the drug release performance was greatly affected by the polymer and pore forming agent used in preparation of pellets.

**KEY WORDS**

Indapamide, Pellets, Controlled release, extrusion/spheronization.

**INTRODUCTION**

In recent years, considerable attention has been focused on the development of novel drug delivery system (NDDS). The reason for this paradigm shift is the low development cost and time required for introducing a NDDS, as compared to new chemical entity. In the form of NDDS, an existing drug molecule can get a new life, thereby

increasing its market value, competitiveness, and product and product patent life. Among the various NDDS available in the market, the oral controlled release system hold a major because of their ease of administration and better patient compliance<sup>1</sup>.

In the conventional oral drug delivery, which is convenient method to achieve both local and systemic effects, there is a little or no

control over drug release from dosage forms. An effective concentration at the target site can be achieved by intermittent administration of grossly excessive dose, which result in constantly changing, unpredictable, and often sub or supra therapeutic plasma concentration, leading to marked side effects<sup>2</sup>.

Controlled release delivery systems provide a uniform concentration or amount of drug at absorption site and thus after absorption, allow maintenance of plasma concentration within a therapeutic range, which minimizes side effects and also reduces frequency of administration. These products typically provide benefits over immediate release formulations, including greater effectiveness, in the treatment of chronic conditions, reduced side effects, and greater patient convenience due to simplified dosing schedule<sup>3,4</sup>.

A number of design options are available to control or modulate drug release from a dosage form. In present research work, micro porous pellets system has been designed for Indapamide.

## **MATERIALS AND METHODS**

### ***Materials***

Indapamide was a gift sample from Microlabs, Bangalore, India. Avicel PH 101 was obtained from Sigma-Aldrich, USA. Sodium Chloride (NaCl) was obtained from Loba Chemie, Mumbai and all other chemicals used were of analytical grade.

### ***Methods***

### ***Preparation of pellets***<sup>5</sup>

The powdered MCC and Sodium Chloride were passed through a 40 mesh sieve. The powders were granulated with water to get a good dough mass of extrudable consistency. The volume of the binder required was noted and the quantity of the binder used was calculated. The wet mass was extruded in to short cylinders using a cylinder roll type gravity feed extruder with a roller speed setting of 100 rpm.

A granulating cylinder with 1.0 mm pore size was used and extrudates were obtained. Spheronization of the extrudates was carried out in the spheronizer using a serrated plate. The spheronization speed was varied to get pellets of good sphericity (Table 1). Drying of pellets was carried out in a tray drier.

### ***Drug loading into pellets***<sup>6</sup>

Dried pellets were collected and the NaCl fraction was removed from the pellets by aqueous extraction: 30g of pellets were placed on to a 500 mL bottle top filter (membrane filter). The filter was placed on a 2-L flask and connected to a vacuum pump. An aliquot of 2 L of water was poured on to the filter in steps of 250 mL to extract the NaCl fraction. Later the pellets were oven dried at 40°C.

The drug was loaded by dipping method i.e. immersing the pellets into the drug solution. It is done by immersing 1g of pellets into the 2.5% indapamide in methanol solution for 24 hrs. After 24 hrs the pellets were collected and oven dried at 40°C. The formulation chart was shown in Table 1.

**Table 1**  
**Formulation chart of prepared pellets.**

Formulation code	Drug %	MCC %	NaCl %
F1	2.5	90	7.5
F2	2.5	80	17.5
F3	2.5	70	27.5
F4	2.5	60	37.5
F5	2.5	50	47.5
F6	2.5	40	57.5
F7	2.5	30	67.5

### **Characterization of Pellets <sup>7</sup>**

**Particle size analysis :** The particle size of the prepared pellets was measured using a Malvern Mastersizer 2000 version 5.1 (Malvern, UK.) The drug loaded Indapamide pellets were dispersed in 1:20 with methanol and measured at temperature of 37°C.

### **Micromeritic properties <sup>8</sup>**

Tap densities of the prepared pellets were determined using Tap densities Tester and percentage Carr's index was calculated.

#### **a. Angle of repose**

Angle of repose was assessed to know the flowability of pellets, by a fixed funnel method. A funnel with the end of the stem cut perpendicular to its axis of symmetry was securely arranged above the graph paper of height which was placed on a flat horizontal surface. Indapamide pellets were carefully poured through the funnel until the apex of the conical pile just reaches the tip of the funnel.

$$\text{Angle of repose } (\theta) = \tan^{-1} (h / r)$$

$$\text{Carr's index} = \frac{(\text{Tapped density} - \text{Bulk density})}{\text{Tapped density}}$$

### **Scanning Electron Microscopic (SEM) studies**

The radius (r) and height of the pile (h) were then determined. The angle of repose ( $\theta$ ) for samples were calculated using the formula,

Angle of repose represents whether the given sample was free flowing or not.

#### **b. Compressibility**

Carr's index is a dimensionless quantity, which proved to be useful to the same degree as the angle of repose values for predicting the flow behavior. Apparent bulk density was determined by pouring the bulk samples into a graduated cylinder. Tapped density was determined by placing a graduated cylinder containing a known mass of powder on a mechanical tapper apparatus (Electro lab tap density tester). Samples were tapped until no further reduction in volume of the sample was observed. Carr's index is calculated using the formula given below and the relationship between compressibility and flow property is shown in Table 5. The mean of three determinations was used to calculate the compressibility index from each of the formulation.

SEM photographs were taken with a scanning electron microscope Model Joel-LV-5600, USA, at the required magnification

at room temperature. The photographs were observed for morphological characteristics and to confirm spherical nature of the pellets.

### **Study of Compatibility<sup>9</sup>**

FT-IR spectroscopy was employed to ascertain the compatibility between indapamide and the selected polymers. The FTIR spectra of the samples were obtained using FT– infrared spectrophotometer (Shimadzu-8400 S, Japan) by KBr pellet method in the wave number range 600 cm<sup>-1</sup>-4000 cm<sup>-1</sup>.

### **Differential Scanning Calorimetry (DSC )<sup>10</sup>**

DSC is a technique in which the difference in heat flow between the sample and a reference is recorded versus temperature All dynamic DSC studies were carried out on Du Pont thermal analyzer with 2010 DSC module. Calorimetric measurements were made with empty cell as the reference. The

instrument was calibrated using high purity indium metal as standard. The dynamic scans were taken in nitrogen atmosphere at the heating rate of 10<sup>o</sup>/min. The runs were made in triplicate. The scanning temperature for reference pure drug and formulation are the same when dynamic measurements are performed, and hence the required heat energy for chemical transformation is directly recorded on a heat flow versus temperature graph. The energy is measured as Joules per kilocalorie.

### **Evaluation of Pellets**

#### **Percentage yield<sup>11</sup>**

The yield was determined by weighing the Indapamide pellets and then finding out the percentage yield with respect to the weight of the input materials, i.e., weight of drug and polymers used. The formula for calculation of percentage yield is as follows;

$$\text{Percentage yield (\%)} = \frac{\text{Wt of pellets}}{\text{Wt. of drug +Wt of polymers}} \times 100$$

### **Drug loading and encapsulation efficiency<sup>12</sup>**

Drug loading is important with regard to release characteristics. Generally, increased drug loading leads to an acceleration of the drug release. Drug entrapment efficiency represents the proportion of the initial amount of drug, which has been incorporated into the pellets.

100 mg of Indapamide pellets were weighed and transferred to 100 ml volumetric flask containing pH 7.4 phosphate buffer. From this, 1 ml of solution was transferred to 10 ml volumetric flask and diluted up to the mark. Further 1 ml of this solution is diluted to 10 ml and absorbance was measured at 236.5 nm. The drug content was calculated by using the formula

$$\text{Amount of drug} = \frac{\text{Conc. from standard graph}}{1000} \times \text{Dilution factor}$$

Percentage encapsulation efficiency is found out by calculating the amount of drug present in 100 mg of pellets. It is further calculated by using formula

$$\text{Percentage Encapsulation Efficiency (\% EE)} = \frac{(b)}{a} \times 100$$

Where, a is the theoretical drug content and b is the drug entrapped.

### **In vitro drug release studies<sup>13</sup>**

The *in vitro* release of drug from the pellets was carried out in basket type dissolution tester USP XXIII, TDT-08L, with auto sampler containing 900 ml of pH 1.2 buffer for the first 2 hrs and in pH 7.4 phosphate buffer for the

next 22 hrs with 100 rpm at  $37 \pm 0.5^\circ\text{C}$ . 10 ml of the sample was withdrawn at suitable time interval and the same volume was replaced with pre-warmed fresh dissolution media. Samples were analyzed for drug content by UV Visible spectroscopy at 264 nm. Dissolution studies were carried out for all the batches of the prepared formulations and commercial formulation.

## RESULTS AND DISCUSSION

Evidence has been proved in recent years MCC possess physical properties and behaviour suitable to prepare gastro resistant, biocompatible, biodegradable porous pellets to release the entrapped drug in the intestinal lumen. In the present study, extrusion/spheronization method was optimized by using MCC, NaCl to entrap the drug. The present method is quite different from other methods. Indapamide is water insoluble drug could be entrapped into water insoluble polymer by extrusion/spheronization method and porous pellets were prepared.

The pellets were prepared by using Avicel PH 101, as polymer and sodium chloride (NaCl), as a pore forming agent by extruder/spheronization technique. When the ratio of MCC was 70 % w/w produces spherical and hard pellets, suitable for pharmaceutical uses. But, when the ratio of MCC was 90 %, 80 %, 50 %, 40 %, 30 % w/w produces rod shaped, egg shaped, semi-spherical and brittle pellets respectively. These pellets not suitable for pharmaceutical purpose. In the present study it was found that the ratio of MCC was 70 % w/w, resultant pellets did not have any surface irregularities and non-aggregated.

An attempt was made to prepare porous pellets using 10 %, 20 %, 40 %, 50 %, 60 %, 70 % w/w of NaCl as a pore forming agent which fail to produces the required pores in the porous pellets. The high amount and low amount of NaCl is responsible for shrinking of

pore in the pellets. It was found that maximum drug load was obtained, when the optimum ratio of 30 % w/w NaCl was used as pore forming agent which produces suitable pore to entrap more amount of the drug.

In the present study, it was found that optimum spheronization speed was found to be 1250 rpm to produce spherical pellets. It was observed that with increase in stirring speed from 1250 rpm to 1500rpm there was a decrease in average size of the pellets and produces semi spherical pellets. When the stirring speed was 1000 rpm, 700 rpm and 300 rpm it produces semi spherical, egg shaped and rod shaped pellets respectively. It was also found that optimum stirring time was found to be 15 min to produce spherical pellets. When the stirring time was 20 min, there was a decrease in yield and produces semi-spherical pellets. When the stirring time was 10 min, 5 min and 2 min, it was observed that some amount of wetted mass adhere to the spheronizer resulting in lower recovery of yield and produces semi spherical, egg shaped and rod shaped pellets respectively. Repeat batches treated at an optimized rate mentioned above, proved to produce reproducible sizes, showing that stirring speed and stirring time were well controlled. In the present study, to produce the spherical porous pellets, an optimum drug concentration 2.5 % w/v was used. It was found that higher the amount of drug will show presence of crystals on surface of pellets which is determined by SEM study which were unsuitable for pharmaceutical uses.

### **Characterization**

The characterization of pellets, micromeritic properties such as particle size analysis, angle of repose, tapped density; granule density and carr's index were found to be within the limits. The obtained results are shown in Table.2

Table 2

*Micromeritic properties and Particle size analysis*

Formulation code	Average size ( $\mu\text{m}$ )	Angle of repose $\theta^0$	Tapped density ( $\text{g}/\text{cm}^3$ )	Granule density ( $\text{g}/\text{cm}^3$ )	Carr's index (%)	Friability (%)
F1	1135 $\pm$ 0.56	26.54 $\pm$ 0.92	0.841 $\pm$ 0.64	1.063 $\pm$ 0.88	9.12 $\pm$ 0.32	0.53 $\pm$ 0.78
F2	1189 $\pm$ 0.45	25.42 $\pm$ 0.25	0.865 $\pm$ 0.92	1.075 $\pm$ 1.78	8.79 $\pm$ 0.99	0.52 $\pm$ 0.45
F3	1245 $\pm$ 0.23	23.45 $\pm$ 0.88	0.902 $\pm$ 1.43	1.056 $\pm$ 1.45	9.39 $\pm$ 0.53	0.43 $\pm$ 0.82
F4	1239 $\pm$ 0.55	26.30 $\pm$ 0.65	0.893 $\pm$ 1.01	1.058 $\pm$ 0.96	8.93 $\pm$ 0.98	0.47 $\pm$ 0.36
F5	1211 $\pm$ 1.02	25.25 $\pm$ 0.46	0.834 $\pm$ 0.55	1.049 $\pm$ 0.72	8.76 $\pm$ 1.76	0.45 $\pm$ 0.78
F6	1229 $\pm$ 0.92	25.98 $\pm$ 0.74	0.839 $\pm$ 0.82	1.072 $\pm$ 0.81	8.69 $\pm$ 2.01	0.49 $\pm$ 0.22
F7	1213 $\pm$ 0.36	24.66 $\pm$ 0.45	0.842 $\pm$ 0.62	1.081 $\pm$ 0.18	8.85 $\pm$ 1.11	0.55 $\pm$ 0.91

**Scanning electron microscopy**

Scanning electron microscopy (SEM) is one of the most commonly used method for characterizing drug delivery systems, owing in large part of simplicity of samples preparation and ease of operation. Scanning electron microscopy was carried out in order to characterize surface morphology, texture and porosity of the coating films. In this study the sample was prepared by placing the formulation F4 samples in pH 7.4 buffer solutions for 24 hr followed by drying the samples at 30° C for 24 hr. The samples were mounted on aluminium mount and sputtered with gold. Sample was scanned at an accelerating voltage of 20 kV. Scanning

electron micrographs obtained are given in Fig 1 and 2.

Fig 1 shows the surface topography of the pellets, where a smooth surface can be observed with its optimal, spherical shape. It also shows the approximate diameter of pellets ranging from 1.2 mm – 1.4 mm. A small degree of etching on the surface can be observed due to effect of the pH 7.4 phosphate buffer as a dissolution media. Fig 2 shows the SEM micrograph of porous pellets formed of formulation at the resolution of 2000x. The fine pore formation of the dimensions in microns can be clearly observed.

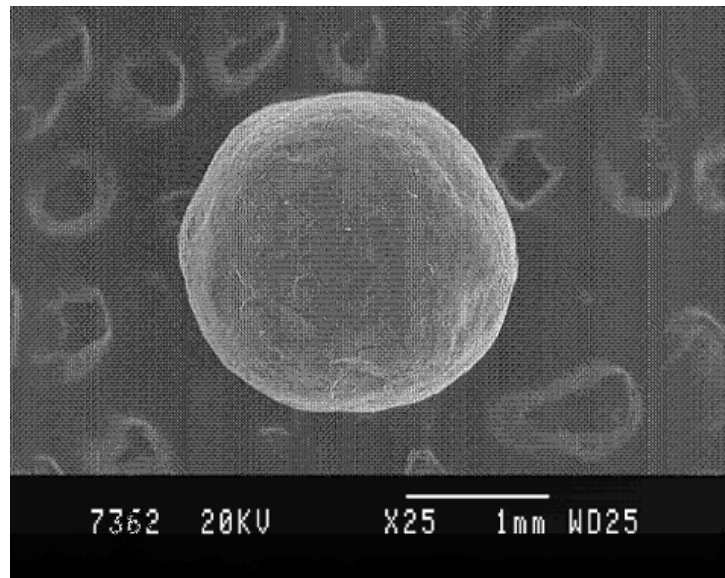


Fig 1

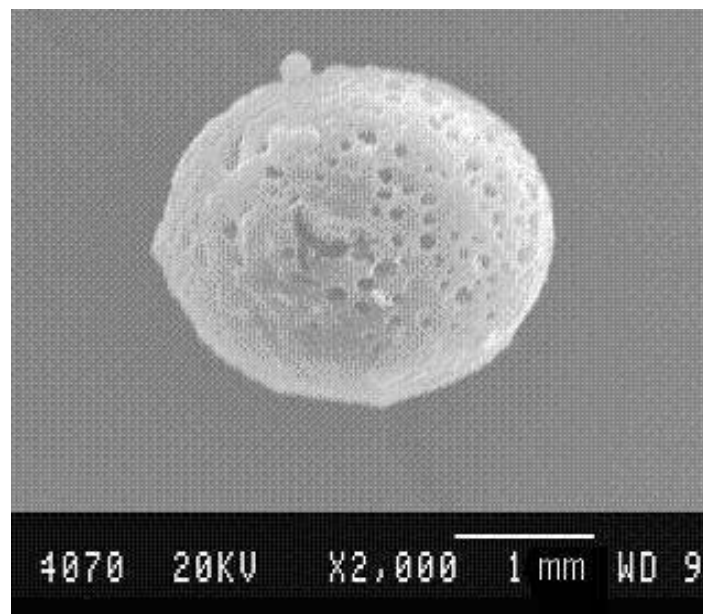
***SEM of non porous pellet***

Fig 2

***SEM of porous pellet******Study of compatibility by FT-IR:***

The compatibility between the drug and polymer was compared by FT-IR spectra. The position of peak in FT-IR spectra of pure Indapamide (Fig 3) is compared with those in FT-IR spectra of Indapamide plus excipients (Fig 4). It was observed that, there was no disappearance or shift in peak position of

Indapamide in any spectra of drug and excipients, which proved that drug and excipients were compatible as shown in Table 3. Hence, it can be concluded that drug can be used with polymer selected without causing instability in the formulation.

Table 3

**Peak positions of pure Indapamide and formulations with intensity range**

Groups	Peak positions in pure drug(cm-1)	Peak positions in formulation Intensity range	
		(cm-1)	(cm-1)
Aromatic C-H stretching	3068.85	3057.6	3030-3200
C-C stretching	1600.0	1589.4	1620
Aliphatic---C-H stretching	2968.55	2972.1	2962-2853
C-H bending	1467.88	1473.66	1485-1445
N-H stretching	3431.8	3446.91	3400
C=C Stretching aromatic	1539.25	1587.8	1450-1600
S=O stretching	1172.76	1183.21	1050-1400

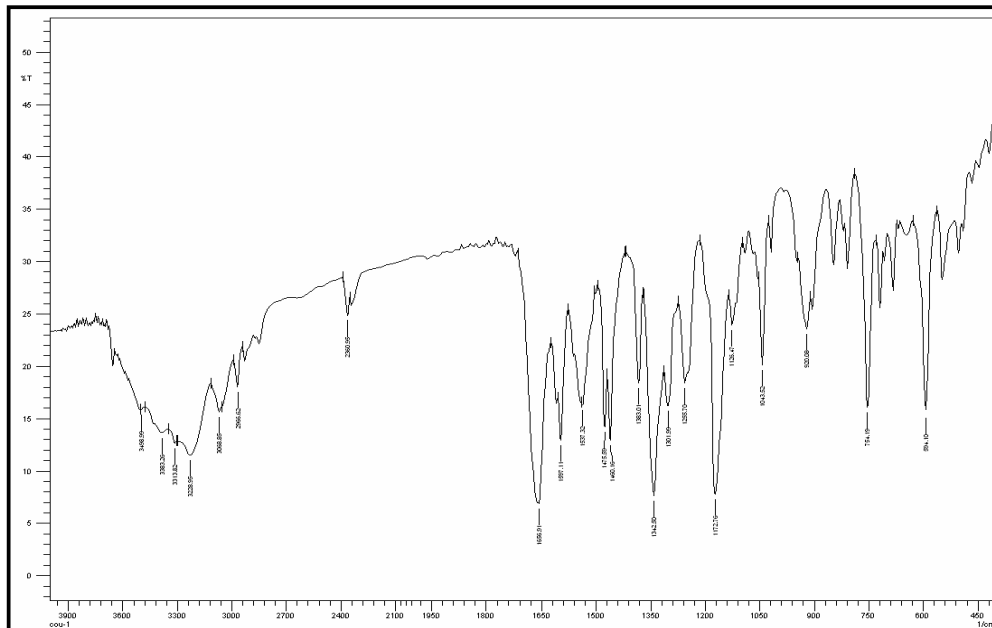


Fig 3

**FT-IR of pure drug (Indapamide)**



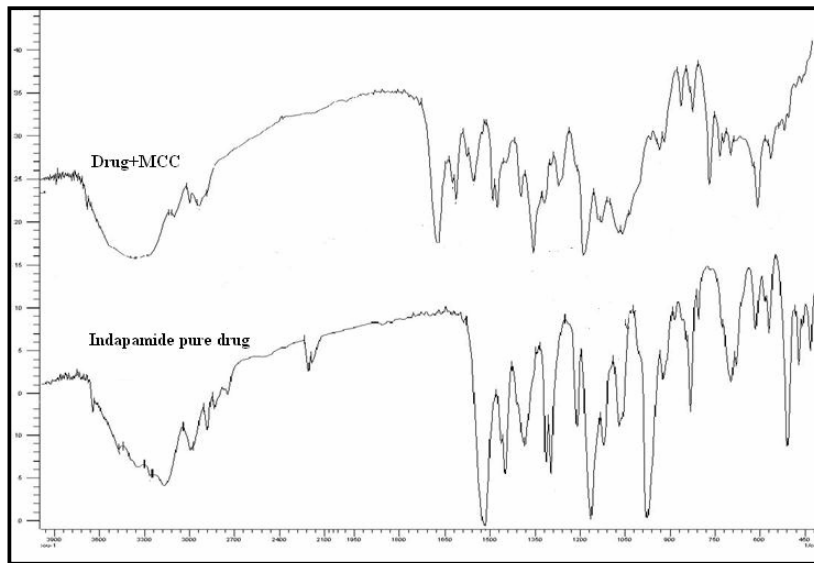


Fig 4

*FT-IR of pure drug with polymer*

**Differential scanning calorimetry (DSC):**

Indapamide exhibits a sharp endothermic peak at 178.25°C. Presence of the endothermic peak at 180.02°C in the drug loaded pellets indicated that there is no interaction between drug and polymer shown in Fig 5 and shown in Table 4.

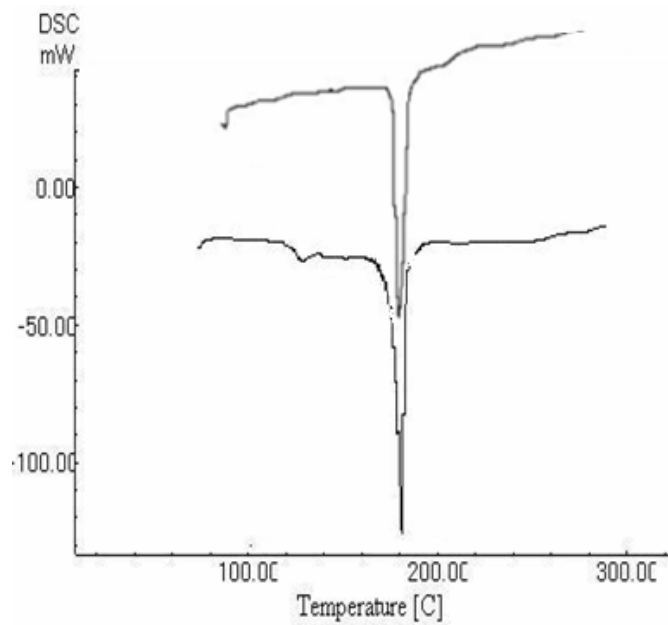


Fig 5

*DSC thermograms of pure drug and polymer.*

Where,  $T_o$  – Onset of melt,  $T_m$  - Melting point and  $T_c$  – Completion of melt

- Indapamide exhibits a sharp endothermic peak at 178.25°C.
- Presence of the endothermic peak at 180.02°C in the drug loaded pellets indicated that there is no interaction between drug and polymer.

**Table 4**

**DSC Results obtained.**

SL. No.	Drug and Formulation	$T_o$	$T_m$	$T_c$	Melting range
1	INDAPAMIDE	173.64	178.25	180.88	7.24
2	FORMULATION	174.35	180.02	183.12	8.92

#### **Determination of Drug Content**

The prepared formulations were analyzed for drug content and it was found to be 89.33 % to 96.5 % for all formulations (Table 5). The drug content for ideal formulation was found

to be 96.5%. The drug content was found to be within the limits which show that the drug was uniformly distributed in all the formulations.

**Table 5**

**Result of % Yield of pellets formulations  $F_1$ - $F_7$**

Sl. No.	Formulation Code	% Yield			
		Trial I	Trial II	Trial III	Mean $\pm$ S.D*
1	$F_1$	89.2	89.5	89.3	9.33 $\pm$ 0.1527
2	$F_2$	93.1	92.4	93.6	93.03 $\pm$ .6027
3	$F_3$	95.7	97.9	96.1	96.5 $\pm$ 1.1718
4	$F_4$	95.8	92.9	93	93.9 $\pm$ 1.6462
5	$F_5$	93.6	95	94.1	94.21 $\pm$ 0.7094
6	$F_6$	96.9	93.8	94	94.9 $\pm$ 1.734
7	$F_7$	96.1	94.7	95	95.23 $\pm$ 0.737

\*Standard deviation, n = 3

#### **Drug loading and encapsulation efficiency of pellets**

The drug loading and encapsulation efficiency of the various formulations were

carried out (Table 6). Among all the formulations,  $F_3$  has shown drug loading and encapsulation efficiency as 19.32 % and 96.33% respectively which is comparatively better than other formulations.

**Table 6**  
**Drug loading and encapsulation efficiency of pellets**

<b>Formulation</b>	<b>Drug loading (%)</b>	<b>Encapsulation efficiency (%)</b>
F1	16.56±0.23	94.50±0.75
F2	16.97±0.65	95.69±0.83
F3	19.32±0.44	96.19±0.33
F4	18.61±0.76	95.98±0.46
F5	18.21±0.53	95.32±0.87
F6	17.12±0.89	94.89±0.64
F7	18.11±0.43	95.10±0.11

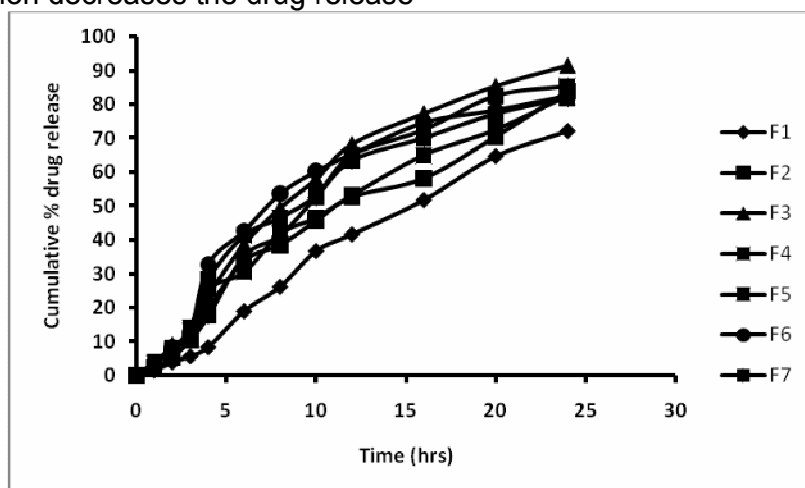
\*Standard deviation, n = 3

### ***In vitro* drug release**

*In vitro* release studies were carried out for all formulations in both acidic and basic media. The *in vitro* release data for the Indapamide formulations are shown in Fig.6

The release profile of pellets in both media clearly indicates that the concentration of polymers and pores formed decreases Indapamide release from pellets. The increase in the concentration of the polymers and decrease in pore concentration decreases the drug release

from the matrices but as the pore concentration and pore size increases it results in immediate release of drug. It was observed that there is no significant release of drug at gastric pH from pellets. At the end of 24<sup>th</sup>, *in vitro* drug release from formulation F1 to F7 was found to be 72.22 % to 91.41 % in the intestinal environment as shown in the Fig 6. The decrease in the drug release from the pellets was due to hydrophobicity of polymer.



**Fig 6**

***In vitro* drug release profile of prepared formulations.**

## CONCLUSION

From the results of our study we can conclude that extrusion/spheronization can produce pellets of appropriate shape and mechanical properties. Prepared pellets varied in pellet properties such as drug dissolution profile, size and shape and flow properties. The drug loading studies shows that immersing the pellets in a drug solution is able to deposit drug inside the porous pellets. The scanning electron micrograph clearly shows the formation of micropores in the pellets. Mathematically fitting

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the release data it was found that drug release from the porous pellets follows fickian diffusion. Porous pellets manufactured by the extracton of NaCl from Avicel PH 101-NaCl pellets can be used as drug carriers.

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