

# Development and evaluation of porous membrane pellets of disopyramide phosphate for sustained release

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**A**im of the present study was to prepare pellets of disopyramide phosphate (DPP) using blend of Hydroxy Propyl Methyl Cellulose (HPMC K4M) and Avicel PH 101 (Microcrystalline cellulose) and to coat the prepared pellets by mixture of Eudragit L100 and Eudragit S100 to obtain microporous membrane for controlled release. Extrusion/spheronization method was employed to produce spherical discrete pellets of uniform size. Solid, porous, discrete, reproducible pellets were obtained. Sieve analysis data indicated that the size of prepared pellets was in the range of 850 – 1180  $\mu\text{m}$ . Yield of pellets was found to be 96.5%. Prepared pellets were spherical in shape, with pores on the surface, as evidenced by scanning electron microscopy (SEM). Compatibility of the drug after encapsulation in the pellets was confirmed by DSC and by FTIR. The prepared pellets were analyzed quantitatively for the drug content and were found to be 96.2%. *In vitro* drug release studies indicated F3C2 as optimized formulation. Formulation F3C2 shows 93.26% drug release up to 12 hrs. 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. *In vivo* study of DPP (300 mg) pellets was carried out in healthy albino rats. Plasma DPP concentrations and other pharmacokinetic parameters were statistically analyzed. The results of paired T-test for the comparison of pharmacokinetic data showed that there was no significant variation between the marketed (Norpace<sup>®</sup> CR) and F3C2. The stability studies performed on F3C2 showed no significant difference in drug content. It was concluded that the drug release performance was greatly affected by microporous membrane coating used in the preparation of pellets.

**Key words:** Disopyramide phosphate, porous membrane, sustained release

## INTRODUCTION

In recent years, considerable attention has been focused on the development of novel drug delivery systems. Among the various novel drug delivery systems, oral controlled release systems hold major because of ease of administration and better patient compliance.<sup>[1,2]</sup> Conventional drug delivery systems have little control over the release of drug and no control over the effective concentration at target site.<sup>[3]</sup> Uncontrolled rapid release of drug cause local irritation or systemic toxicity.<sup>[4]</sup> By using oral controlled drug delivery, system can provide continuous delivery of drugs at predictable and reproducible kinetics throughout the GI transit.<sup>[5]</sup>

Oral controlled drug delivery systems broadly fall into two categories: single unit and multiple unit systems.

The multiple-unit dosage forms consist of pellets or microencapsulated drug contained in a capsule or a tablet.

Pellets can be defined as agglomerates of fine powders or granules made up of drugs and pharmaceutical excipients. Pellets range in size typically between 0.5 to 1.5 mm and are mostly preferred for oral route of drug delivery.<sup>[6]</sup>

Pellets offer greater degree of flexibility throughout the design and development of oral dosage forms. They can be divided into different dose strengths without any process changes and can be used to deliver incompatible biologically active agents all together or particles with

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different release profiles at same site or at different site of gastrointestinal tract. Taken orally, pellets usually disperse freely in the gastrointestinal tract and as a result, maximize the drug absorption, minimize local irritation of the mucosa, and reduce patient-to-patient variability.<sup>[7]</sup>

Disopyramide phosphate (DPP), (2*RS*)-4-[bis (1-methylethyl) amino]-2-phenyl-2-(pyridin-2-yl) butanamide dihydrogen phosphate, is a potential cardiac antiarrhythmic agent.<sup>[8]</sup> It is most commonly used in the prevention of post-myocardial infarction ventricular arrhythmias. It is indicated for the treatment of documented ventricular arrhythmias such as sustained ventricular tachycardia, which in the judgment of the physician, are life-threatening.<sup>[9]</sup>

It is available for oral administration in capsules containing 300 mg of disopyramide base, present as a phosphate. It is freely soluble in water, and the free base (pKa 10.4) has an aqueous solubility of 1 mg/mL. The mean plasma half life of this drug in the healthy human is 6 hrs.<sup>[10]</sup>

The use of DPP is associated with adverse reactions: hypotension and congestive heart failure. The most common adverse reactions are dry mouth, urinary hesitancy, constipation, blurred vision, urinary retention, muscle weakness, malaise, nausea, impotence.<sup>[11]</sup>

A number of design options are available to control or modulate drug release from a dosage form. In present research work, porous membrane pellets system has been designed for DPP thus reducing the dosing frequency confirming more patient compliance.

## MATERIALS AND METHODS

### Materials

DPP was obtained from Sigma Aldrich Mumbai, India. Microcrystalline cellulose and HPMC K4M were procured from Loba chemie Pvt. Ltd., Mumbai, India. Eudragit L100 and S100 were obtained from Evonik Degussa, Mumbai. All other chemicals and solvents used were of analytical grade.

### Methods

#### *Preparation of disopyramide phosphate pellets by extrusion-spheronization method*

The drug (Disopyramide phosphate), powdered MCC and polymer (HPMC K4M) were passed through a 40 mesh sieve. The powders in different ratios were granulated with water to get a good dough mass of extrudable consistency. 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 from 300 rpm to 1500 rpm and spheronization time was varied

from 5 min to 25 min to get pellets of good sphericity as shown in Table 1. Drying of pellets was carried out in a tray drier.<sup>[12]</sup>

#### *Coating of prepared pellets*

Eudragit L100 and Eudragit S100 in varying concentrations are used for coating trials on 50 g of pellets. The required quantities of polymers were dissolved in acetone solvent using triethyl citrate (TEC) as a plasticizer. The solutions were then filtered through a nylon cloth before coating. Different coating compositions are shown in Table 2.

#### *Characterization of pellets*

##### *Particle size analysis*

The particle size distribution of pellets was carried out by sieve analysis<sup>[13,14]</sup> using a set of US standard sieves. Sieves of size #14, 16, 18, 22 and 44 were used along with a pellet load of 10 g. The sieve set was then mechanically shaken for 10 min. The net weight retained on each sieve was determined and these values were used for calculation of the particle size distribution.

##### *Micromeritic properties*

###### *Angle of repose*

Angle of repose<sup>[15]</sup> was assessed to know the flowability of pellets by a fixed funnel method. The radius (r) and height of the pile (h) were then determined. The angle of repose ( $\theta$ ) for samples were calculated using the formula,

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

Where, 'r' is the radius of pile and 'h' is the height of the pile.

The mean of three determinations was used to calculate the angle of repose from each of the formulation.

###### *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

**Table 1: Formulation chart for the preparation of pellets**

Formulation code	Drug	HPMC K4M	MCC
F1	30	0	70
F2	30	5	65
F3	30	10	60
F4	30	15	55
F5	30	20	50

**Table 2: Microporous membrane coating of optimized formulation**

Composition	F3C1	F3C2	F3C3	F3C4	F3C5
Eudragit L100: S100	1:1	1:3	3:1	1:0	0:1
Triethyl citrate	2ml	2ml	2ml	2ml	2ml
Acetone (qs)	100ml	100ml	100ml	100ml	100ml

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 (Electrolab tap density tester). Carr's index is calculated using the formula given below. The mean of three determinations was used to calculate the compressibility index from each of the formulation.

$$\text{carr's index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \quad (2)$$

#### *Friability (F)*

Pellets of known mass (particle size 1000–1410  $\mu\text{m}$ ) were placed in a Roche friability tester (Electrolab friability tester, EF-2) and subjected to impact testing at 25 rpm for 5 min. After passing the load through a sieve of mesh size 20 (840  $\mu\text{m}$ ), the weight of material retained on the sieve was determined and the friability was calculated using the following equation:

$$\text{Friability}\% = [1 - W/W_0] \times 100 \quad (3)$$

Where,  $W_0$  is the initial weight and  $W$  is the weight after 100 rotations.

The friability test is performed on the pellets to ensure their mechanical strength. Lower friability values indicate good mechanical strength of the pellets.

#### *Scanning electron microscopic studies*

Scanning Electron Microscopic (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.

#### *Pellet sphericity*

Pellet size and shape were determined using an image analysis system.<sup>[16]</sup> Photomicrographs were taken with a digital camera. The obtained images were processed by image analysis software (Digimizer, USA) to characterize each individual pellet by aspect ratio (AR) and two-dimensional shape factor ( $eR$ ).

$$eR = 2\pi r/Pm - (b/l)^2 \quad (4)$$

Where,  $r$  is the radius,  $Pm$  is the perimeter,  $l$  is the length and  $b$  is the width of the pellet.

#### *Compatibility studies*

Drug is in intimate contact with one or more excipients, which could affect the stability of the drug. The knowledge of the drug-excipient interactions is essential for selecting appropriate excipients. This was studied using FT-IR spectrophotometer and Differential Scanning Calorimetry (DSC).

#### *Differential scanning calorimetry*

All dynamic DSC studies were carried out on DuPont thermal analyzer with 2010 DSC module. The dynamic scans were taken in nitrogen atmosphere at the heating rate of 10°C/min. The runs were made in triplicates.

#### *Fourier transform infrared spectroscopic (FT-IR) studies*

FTIR analysis was carried out for pure drug and for pellets using KBr pellet method on FTIR spectrophotometer. Drug was mixed with KBr and spectra was taken. FT-IR spectrum of pure drug DPP was compared with FT-IR spectra of DPP formulations. Disappearance of peaks or shifting of peaks in any of the spectra was studied using the apparatus FTIR-8400-S, Shimadzu, Japan.

#### *Evaluation of pellets*

##### *Percentage yield*

It determines whether the preparation procedure chosen for preparation of pellets is efficient and is of prime importance. The amount of active compound, polymer, MCC, and other process parameters are deciding factors for the yield of the product during the preparation of pellets.

The formula for calculation of % yield<sup>[17]</sup> is as follows:

$$\% \text{ yield} = \frac{\text{wt of pellets}}{\text{wt of drug} + \text{wt of polymers}} \times 100 \quad (5)$$

##### *Drug content*

Drug content<sup>[18]</sup> of pellets was estimated using UV/visible spectrophotometric method. Pellets were crushed to powder. Finely crushed sample equivalent to 100 mg of DPP was transferred to 100 ml volumetric flask and diluted to 100 ml with methylene chloride : methanol (50:50 v/v) and kept on a rotary shaker for 24 hrs for complete extraction of the drug from the pellets. Solution was filtered; 1 ml of this solution was taken, diluted to 100 ml with methylene chloride: methanol (50:50 v/v) and absorbance was noted at 265 nm. Drug content was determined using calibration curve. All the trials have been done in triplicate. ( $n = 3$ )

##### *Loose surface crystal study (LSC)*

A total of 200 mg of pellets was suspended in 100 ml of phosphate buffer (pH 7.4). The amount of drug was analyzed spectrophotometrically at 265 nm.<sup>[19]</sup>

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

The *in vitro* release of drug from the coated pellets was carried out in basket type dissolution tester USP XXIII, TDT-08L, containing 900 ml of pH 1.2 buffer for the first 2 hrs, and in 6.8 pH for next 3 hrs, and 7.4 pH phosphate buffer for rest of the studies.<sup>[20]</sup> The volume of the dissolution media was maintained at 900 ml with constant stirring (100 rpm) and temperature of bath was maintained at  $37 \pm 0.5^\circ\text{C}$ . Aliquots (10 ml) of dissolution media were sampled at specified time points and

replaced with fresh media immediately after sampling. Samples were analyzed for drug content by UV visible spectroscopy. The release data obtained were fitted into various mathematical models to know which mathematical model is best fitting for the obtained release profile.

#### Mathematical model fitting

The release data was fitted into various mathematical models using PCP.Disso-V2.08 software to know which mathematical model will best fit the obtained release profile. The parameters like 'n' the time exponent, 'k' the release rate constant and 'R' the regression co-efficient were determined to know the release mechanisms.

The value of 'n' determined from Korsmeyer-Peppas equation if found to be below 0.45, it indicates that the drug release from the formulation follows Fickian diffusion, if 'n' value is between 0.5-0.85, indicates Non-Fickian diffusion or anomalous mechanism (relaxation controlled) and if 'n' value is above 0.89, indicates super case II transport.

#### In vivo studies

##### Ethical review

The project proposal has been cleared and approved by Institutional animal ethical committee, J.S.S. College of pharmacy, Mysore (Code: 078/2011).

##### Study design

Ten healthy albino rats were selected for the *in vivo* study. The formulation F3C2 was selected in order to study *in vivo* performance of the preparation, on the basis of *in vitro* release studies.<sup>[21,22]</sup>

Albino rats of similar weight were selected for *in vivo* studies, kept in well-spaced ventilated cages, and the rats were kept on fast for a day. The animals were divided into three groups of three animals each. The first group was served as a placebo (without any treatment), and the second group received the suspension of marketed formulation Norpace® CR (Control group i.e., standard) in water, and the third group was given the suspension of formulation (F3C2) (Test group) in water. The doses were given orally with the help of cannula. Blood samples were collected from retro-orbital vein at 0 (pre-dose interval), 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 10, 12, 16, 20, and 24 hrs post dose intervals. The contents were centrifuged (REMI motors) at 1500 rpm for 10 mins, and the supernatant liquid was separated and the drug content was determined using HPLC.

##### Extraction procedure

Plasma was separated from formed elements of blood by centrifuging. Add 50  $\mu$ l of the internal standard (*p*-chlorodisopyramide) solution, 50  $\mu$ l of sodium hydroxide (10 mol/L), and 4 ml of dichloromethane to 500  $\mu$ L of plasma sample in a centrifuge tube. Mix for 5 min with rotary mixer and centrifuge at 1500 rpm for 10 min. Discard the aqueous phase. Transfer 2 ml of

dichloromethane layer to a clean centrifuge tube, add 50  $\mu$ l of acetic anhydride, and evaporate to dryness at 40°C. The residue was re-suspended in 100  $\mu$ l of mobile phase and 25  $\mu$ l was injected to the column. Quantification was achieved by the measurement of the peak area ratio of the DPP to the internal standard (*p*-chlorodisopyramide). The limit of detection of plasma was 100 ng/ml (500  $\mu$ L of plasma injected).

##### Chromatographic conditions

The mobile phase consisting of Methanol: Acetonitrile: THF were filtered through 0.45  $\mu$  Ultrapor N66 Nylon membrane solvent filter, degassed and were pumped from the solvent reservoir in ratio of 55:45:5, v/v/v and was pumped into the column. Mobile phase flow rate was maintained at 1.0 ml/min with a detection wavelength set at 265nm. Volume of injection loop was 20  $\mu$ l. The column and the HPLC system were kept in ambient temperature.

##### Pharmacokinetic and statistical data evaluation

The peak plasma concentration ( $C_{max}$ ) and time needed to reach peak plasma concentration ( $T_{max}$ ) were computed directly from plasma level profiles as a measure of the rate of absorption of drug from each product. The elimination rate constant ( $K_e$ ) was calculated from the elimination phase of logarithm of drug concentrations against time curve. The biological half life ( $t_{1/2}$ ) was determined the relation:

$$t_{1/2} = 0.693 / K_e \quad (6)$$

The extent of absorption for the drug (Norpace® CR and formulation F3C2) from the area under plasma concentration time curve from 0 to 24 hrs ( $AUC_{0-24}$ ) was calculated by the trapezoidal rule method. Area under curve from zero to infinity ( $AUC_{0-\infty}$ ) was calculated using the formula:

$$AUC_{0-\infty} = AUC_{0-24} + C_{24}/K \quad (7)$$

Where,  $C_{24}$  = drug concentrations in plasma at 24 hrs.

##### Stability studies

Optimized formulation of the pellets was selected for stability studies.<sup>[23]</sup> Formulations were packed in a screw capped bottle and studies were carried out for 90 days by keeping at:

- 25 + 2°C and 60 + 5% RH
- 40 + 2°C and 75 + 5% RH

Samples were withdrawn on 30 th, 60 th, and 90 th day and were analyzed for drug content spectrophotometrically at 265 nm.

## RESULTS AND DISCUSSION

### Optimization of process parameters for pelletization

In the present study, extrusion/spheronization method was optimized in order to prepare pellets. Table 3 shows



the results of optimization of extrusion/spheronization process.

In the formula optimization study, we found that as the concentration of polymer was increased, the granulating mass became elastic and extrudes were not formed. At very low concentrations of polymer, spheroids were formed but a major fraction of the particles was irregular in shape. Also, the spheronized mass had a wide range of size distribution that was not ideal. Hence, Drug-MCC-Polymer ratio of 30:60:10 was selected.

In the optimization of spheronization speed, we found that at lower speeds, more numbers of rod and dumbbell-shaped particles were obtained. At higher speeds, due to centrifugation, spheronization did not occur properly, again leading to the formation of rod- and dumbbell-shaped particles. The optimum spheronization speed was found to be 900 rpm to produce spherical pellets.

In the optimization of spheronization time, we found that at lower spheronization times (i.e., less than 15 min), a major portion of the wetted mass adhere to the spheronizer resulting in lower recovery of yield and produces semi spherical, egg shaped, and rod shaped pellets, respectively, and at longer residence times, there was decrease in yield, due to evaporation of water, the particles were dried and thus, size reduction was observed.

Under the ideal conditions, viz., drug-MCC-polysaccharide ratio of 30:60:10, spheronization time of 15 min at 900 rpm speed, maximum yield of spherical particles was obtained [Table 3].

Further, the optimized formulation (F3) was coated with different ratios of Eudragit S100 and Eudragit L100 polymers to obtain microporous membrane coating of pellets.

### Characterization of pellets

#### Particle size distribution

The measured particle size distribution for the 14/16, 16/18, 18/22 and 22/44 mesh cuts was 22%, 68%, 3%, and 2%, respectively. The particle size results revealed that the process used gave a maximum particle size for the 16/18 mesh cut (68%). About 22% of the pellets were found in the 14/16 mesh cut. The obtained average pellet diameter was in the range 850-1180  $\mu\text{m}$ . Overall, 90% of the pellets obtained were in the desired particle size range proving that the process is very reproducible.

#### Micromeritic properties

The obtained data of angle of repose ( $\theta$ ), tapped density, granular density, % compressibility index (CI) along with related parameters are presented in Table 4. The values of  $\theta$  and CI ranged from  $23.45 \pm 0.8$  to  $26.54 \pm 0.9$  and  $8.76 \pm 1.76$  to  $9.39 \pm 0.53$ , respectively, indicating that the obtained values were well within the limits. This result clearly shows that the prepared pellets have reasonably good flow potential.

**Table 3: Optimization of process parameters for pelletization**

Parameter	Formulation code	Parametric values	Spheroid description
Drug : HPMC : MCC ratio (W/W)	F1	30:0:70	Rod shape
	F2	30:5:65	Spheroids with wide size range
	F3	30:10:60	Spheroids with narrow size range
	F4	30:15:55	Dumbbell shape
	F5	30:20:50	Formation of elastic mass; no extrudes
Spheronization speed (rpm)	F3	300	Dumbbell shape
		600	Egg shape
		900	Spherical
		1200	Semi spherical
		1500	Rod shape
Spheronization time (mins)	F3	5	Rod shape
		10	Egg shape
		15	Spherical
		20	Spherical
		25	Spherical

**Table 4: Micromeritic properties of pellets**

Formulation code	Angle of repose ( $\theta$ )	Tapped density ( $\text{g}/\text{cm}^3$ )	Granule density ( $\text{g}/\text{cm}^3$ )	Carr's index (%)	Friability (%)
F1	$26.54 \pm 0.9$	$0.84 \pm 0.64$	$1.06 \pm 0.88$	$9.12 \pm 0.32$	$0.53 \pm 0.78$
F2	$25.42 \pm 0.2$	$0.86 \pm 0.92$	$1.07 \pm 1.78$	$8.79 \pm 0.99$	$0.52 \pm 0.45$
F3	$23.45 \pm 0.8$	$0.90 \pm 1.43$	$1.05 \pm 1.45$	$9.39 \pm 0.53$	$0.43 \pm 0.82$
F4	$26.30 \pm 0.6$	$0.89 \pm 1.01$	$1.05 \pm 0.96$	$8.93 \pm 0.98$	$0.47 \pm 0.36$
F5	$25.25 \pm 0.4$	$0.83 \pm 0.55$	$1.04 \pm 0.72$	$8.76 \pm 1.76$	$0.45 \pm 0.78$

The values of tapped density ranged between  $0.83 \pm 0.55$  to  $0.90 \pm 1.43$  g/cm<sup>3</sup>. Density difference between the formulations is negligible and the density values of formulations were well within the limits, indicating that the prepared pellets were non-aggregated and spherical in nature.

#### Scanning electron microscopy

The SEM microphotograph of the optimized formulation, F3C2, is shown in Figure 1, which shows the surface morphology of the pellets, which have a spherical shape and a smooth surface. It can be seen from the figure that the approximate diameter of pellets ranges from 1.0 to 1.2 mm. Figure 2 shows the SEM microphotograph of the surface of the pellets (F3C2) where pores are formed due to the leaching of Eudragit L-100 above pH 5.5. The fine pore formation in microns can be clearly observed.

#### Pellet sphericity

From the photomicrograph image analysis, calculated aspect ratio (AR) and two-dimensional shape factor (*eR*) were found to be 1.042 and 0.948, respectively. The obtained *eR* and AR values of the pellets were closer to the value of 1, which confirmed that the prepared pellets were spherical in nature.

#### Fourier transform infra red spectrum (FT-IR)

FTIR spectra were obtained for pure DPP and formulation and are presented in Figure 3. Characteristic peaks of pure drug was observed at amide and N-H stretching at 3479.7 and 3294.53 cm<sup>-1</sup>, Amide C = O stretch and NH<sub>2</sub> deformation at 1643.41 cm<sup>-1</sup>, whereas in formulation amide and N-H stretching was observed at 3479.5 and 3292.65 cm<sup>-1</sup>, Amide C = O stretch and NH<sub>2</sub> deformation at 1643.32 cm<sup>-1</sup>, respectively. From the data, it is observed that similar characteristic peaks of pure drug and formulation were appearing with minor differences. Hence, it appears there is no chemical interaction between drug and polymer and it can be concluded that the characteristics bands of pure drugs were not affected after successful formulation.

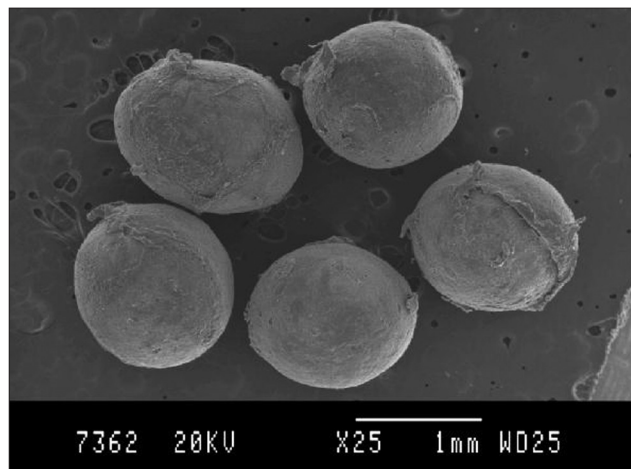


Figure 1: SEM of pellets

#### Differential scanning calorimetric (DSC) studies

To understand the compatible state of the drug, DSC studies were carried out on pure drug and formulation (pellets). The thermograms obtained are shown in Figure 4. DPP exhibits a sharp endothermic peak at to 212.25°C. It was observed that presence of the endothermic peak at 214.36°C in the pellet formulation indicated, that the drug retains its identity in the prepared pellets. Presence of the endothermic peak at 214.36°C in the pellet formulation indicated that there is no interaction between drug and polymer.

#### Percentage yield

During the process of extrusion/spheronization, the mechanical variables cause loss of final product and hence process yield may not be 100%. Pellets were weighed after drying and the percentage yield was calculated. Among all formulations showed higher % yield. The data obtained is shown in Table 5.

#### Evaluation of the pellets formulation

##### Determination of drug content

The prepared formulations were analyzed for drug content and the data is reported in Table 6. The drug content was found to be within the limits which show that the drug was uniformly distributed in all the formulations.

##### Loose surface crystal study

The amount of surface drug determined by loose surface crystal study was found to be minimal (0.82-2.3%).

##### In vitro drug release study

*In vitro* release studies were carried out for all formulations in pH 1.2, pH 6.8, and pH 7.4 buffers as shown in Figure 5. It was observed that there was no significant release of drug at gastric pH 1.2 from pellets. At the end of 5<sup>th</sup> hr, drug release from F3C1 was found to be  $59.45 \pm 0.11\%$ , F3C2 ( $40.05 \pm 0.74\%$ ), F3C3 ( $62.34 \pm 0.48\%$ ), F3C4 ( $79.03 \pm 0.62\%$ ), and F3C5 ( $20.78 \pm 0.31\%$ ), respectively. At the end of 12<sup>th</sup> hr, *in vitro* drug release from formulation F3C2 and F3C5 were found to be  $93.26 \pm 0.31\%$ ,  $75.39 \pm 0.28\%$ . From the *in vitro* release data, F3C2 was selected

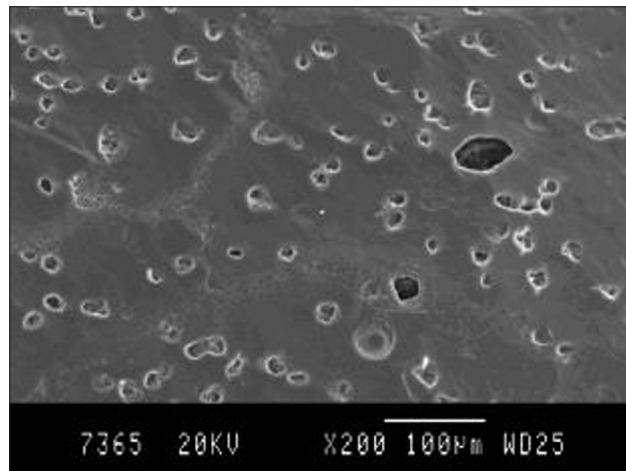


Figure 2: SEM of microporous membrane

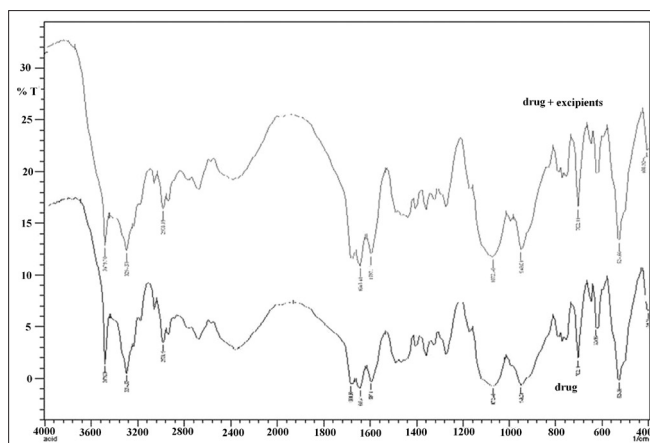


Figure 3: FT-IR of pure drug and formulation

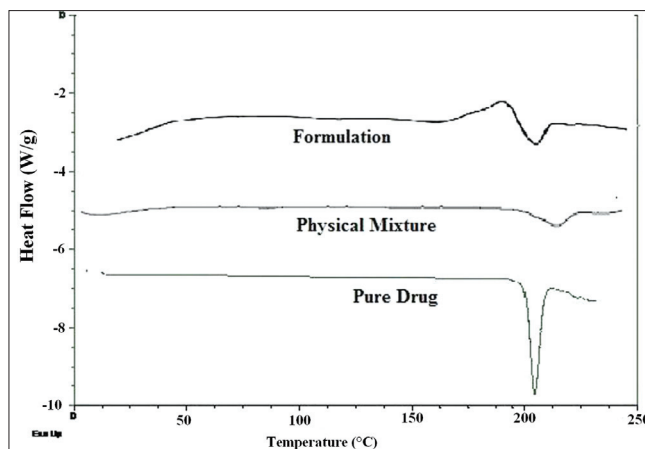


Figure 4: Comparison of DSC thermogram of pure drug and formulation

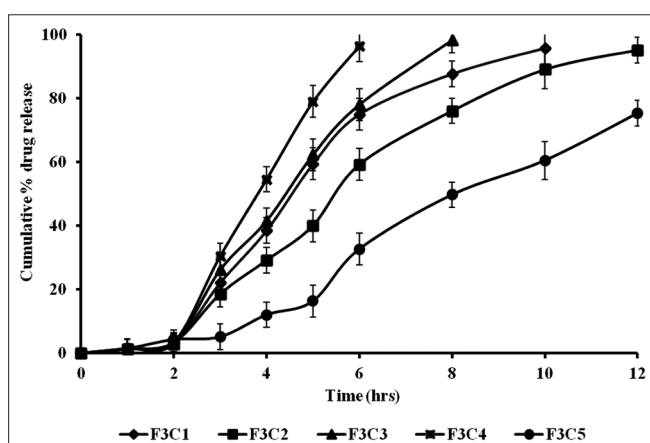


Figure 5: % cumulative drug release (F3C1-F3C5)

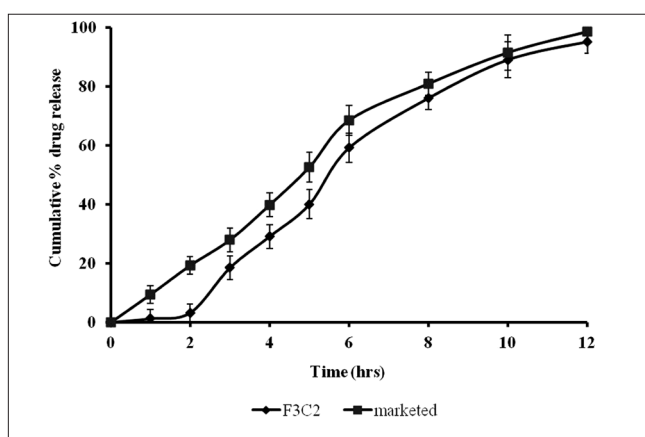


Figure 6: % cumulative drug release of F3C2 and Norpace® CR

Table 5: % Yield of pellets formulations F1 to F5

Formulation	% Yield $\pm$ SD*
F1	90.33 $\pm$ 0.15
F2	93.9 $\pm$ 1.64
F3	96.5 $\pm$ 1.15
F4	94.2 $\pm$ 0.7
F5	93.03 $\pm$ 0.6

as an optimized formulation due to its sustained release behavior upto 12 hrs. The sustained release behavior is due to slow diffusion of drug through the porous membrane.

#### Comparison with a marketed product

Formulation F3C2 was compared with a marketed product Norpace® CR. In Figure 6, the percentage of drug released from Norpace® CR and F3C2 is plotted as a function of time. It is evident that prepared DPP pellets showed sustained release upto 12 hrs as compared to marketed formulation, Norpace® CR

#### Mathematical model fitting of obtained drug release data

The data obtained from dissolution study of F3C2 formulation was fitted into various release kinetics models as shown in

Table 6: Drug content of pellets formulation, F3

Formulation code	Trials	% drug content	% drug content Mean $\pm$ SD
F3	Trial 1	96.5	96.2 $\pm$ 0.36
	Trial 2	95.8	
	Trial 3	96.3	

\*Mean  $\pm$  SD, n = 3

Table 7. The data was also fitted into Korsmeyer-Peppas model in order to obtain the 'n' value to describe the mechanism of drug release. The 'n' value of 0.765 indicates that the drug release follows anomalous (non-Fickian) diffusion mechanism, which signifies that the drug release is both diffusion-controlled and swelling-controlled.

#### In vivo study

The mean plasma concentration time profiles and comparative mean pharmacokinetic parameters of DPP following the administration of the two products (Norpace® CR and formulation F3C2) are shown in Figure 7 and Table 8.

After oral administration, the highest mean  $C_{max}$  values were observed for both Norpace® CR ( $4967 \pm 53.71$  ng/ml) and formulation F3C2 ( $4836 \pm 24.31$  ng/ml). However, the

difference in the  $C_{max}$  values recorded for both the products was statistically insignificant. The peak plasma levels were observed to be within the range from 4913 ng/ml to 5020 ng/ml for Norpace® CR, from 4811 ng/ml to 4860 ng/ml for F3C2. Comparison of the mean concentration time curve of both products indicated that formulation F3C2 is associated with significant lower peak plasma concentration than that of Norpace® CR. In addition, the mean plasma concentrations of DPP for both the products in all subjects were within the therapeutic window (1500-5000 ng/ml). The time taken to reach peak plasma concentration  $t_{max}$  was 3 hrs and 4 hrs for Norpace® CR and F3C2, respectively.

Mean  $K_a$  for Norpace® CR and F3C2 were found to be  $0.381 \pm 0.002h^{-1}$  and  $0.362 \pm 0.003h^{-1}$ , respectively and the difference between the products was statistically insignificant. Mean  $K_e$  for Norpace® CR and F3C2 were found to be  $0.138 \pm 0.003h^{-1}$  and  $0.143 \pm 0.004h^{-1}$ , respectively. The mean elimination half life  $t_{1/2}$  for Norpace® CR and formulation F3C2 were found to be  $5.02 \pm 0.02$  hrs and  $4.82 \pm 0.03$  hrs, respectively. The difference between the  $K_e$  and  $t_{1/2}$  values obtained was not statistically significant.

The mean  $AUC_{0-24}$  values for Norpace® CR and F3C2 were found to be  $48670.3 \pm 132.87$  ng/ml  $h^{-1}$  and  $46537 \pm 40.04$  ng/ml  $h^{-1}$ . From the result, statistical analysis indicated that F3C2 exhibited a smaller and non-significant reduction in the AUC values than Norpace® CR. The slower *in vitro* release of DPP from the Norpace® CR and F3C2 may be responsible for the decreased AUC values. The observed mean  $AUC_{0-\infty}$  values for Norpace® CR and F3C2 were  $51551.1 \pm 129.22$  ng/ml. $h^{-1}$  and  $49418.1 \pm 46.88$  ng/ml h, respectively, and no statistical significant difference were observed.

**Table 7: Data of various parameters of model fitting of F3C2 pellet formulation**

Model fitting	Regression coefficient, R <sup>2</sup>
Zero	0.9726
First	0.8479
Higuchi	0.8672
Peppas	0.9418
Order of drug release	Zero order
Mechanism of drug release	Peppas
Diffusion exponent Peppas model	$n = 0.765$

**Table 8: Statistical comparison of mean values of pharmacokinetic parameters**

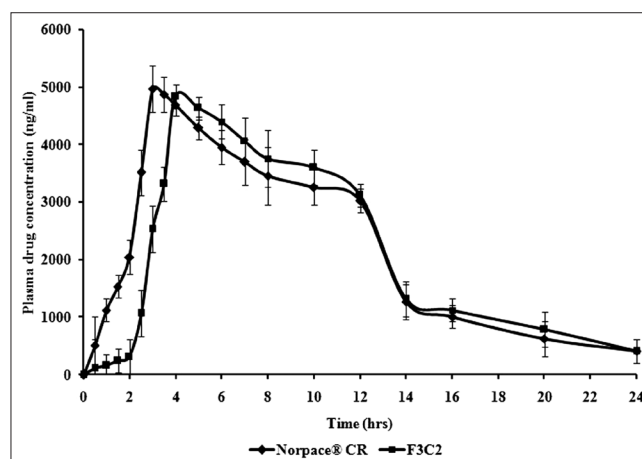
Parameters	Norpace® CR	F3C2	P value
$t_{max}$	3.0h	4.0h	< 0.05
$C_{max}$	$4967 \pm 53.71$ ng/ml	$4836 \pm 24.31$ ng/ml	< 0.05
$t_{1/2}$	$5.02 \pm 0.02$	$4.82 \pm 0.03$	< 0.05
$AUC_{0-24}$	$48670.3 \pm 132.87$ ng/ml $h^{-1}$	$46537 \pm 40.04$ ng/ml $h^{-1}$	< 0.05
$AUC_{0-\infty}$	$51551.1 \pm 129.22$ ng/ml $h^{-1}$	$49418.1 \pm 46.88$ ng/ml $h^{-1}$	< 0.05
$K_a$	$0.381 \pm 0.002$	$0.362 \pm 0.003$	< 0.05
$K_e$	$0.138 \pm 0.003$	$0.143 \pm 0.004$	< 0.05

### Stability studies

Stability studies were carried out for F3C2 formulation in order to check any changes in physical appearance and drug content. No significant changes were shown in the physical appearance and drug content of the formulation after storage for 3 months.

### CONCLUSION

DPP pellets were successfully prepared by extrusion/spheronization method and coated the prepared pellets by mixture of Eudragit L100 and Eudragit S100 to obtain microporous membrane controlled release. Pores were formed on the surface of pellets due to the solubilization of Eudragit L100 at certain pH. White spherical pellets with smooth surface were obtained with a yield of 96.5% proving overall superiority of this method. The SEM photograph clearly showed spherical pellets with microporous surface. The DSC and FTIR studies showed that there is no chemical interaction between the drug and polymers. The drug content in pellets was found to be  $96.2 \pm 0.36\%$ . The *in vitro* drug release profile of the formulation F3C2 showed that the drug release was sustained upto 12 hrs as compared to Norpace® CR. The results of mathematical model fitting of data indicated that, the drug release through pellets was through non-Fickian diffusion. Results of the stability studies showed that there were no significant changes in the drug content and physical appearance. The *in vivo* studies showed



**Figure 7:** Plasma drug concentration time curve of F3C2 (Test group) and Norpace® CR (Control group)



similarity in plasma drug concentration time profiles and *in vivo* equivalent behavior.

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