Research Article

Formulation and Evaluation of Delayed Release Pellets of Ivabradine Hydrochloride

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Received: 06-05-2021; **Revised:** 24-06-2021; **Accepted:** 30-06-2021; **Published on:** 15-07-2021.

ABSTRACT

The aim of preset research work is to formulate and evaluate delayed release pellets of Ivabradine HCl. Pellets are prepared using extrusion-spheronization process and the process parameters are optimized. Polymer coating done with Kollicoat SR 30 D as rate controlling polymer and finally enteric coating done with Eudragit L30D-55. Drug release in formulation F1-F9 studied and it found that the low polymer concentration (2 %) was unable to retard the drug release up to 12 hr so concentration increased batch by batch and finally 12 % coating batch gives desired results which retard the drug release up to 12 hr. also found that the drug release was very low after more % coating than the 12 %. Hence based on that the F5 batch was optimized batch and its found stable during stability study of 1 month.Delayed release pellets of Ivabradine HCl was successfully prepared using Kollicoat SR 30 D as rate controlling polymer.

Keywords: Ivabradine HCl, Pellets, delayed release.

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DOI:
10.47583/ijpsrr.2021.v69i01.029

DOI link: http://dx.doi.org/10.47583/ijpsrr.2021.v69i01.029

INTRODUCTION

Pellets are agglomerates of fine powders or granules of mass medications and excipients. They comprise of little, free-streaming, circular or semi-round strong units, normally from around 0.5 mm to 1.5 mm, and are proposed for the most part for oral organization. Inserts of little, clean chambers shaped by pressure from cured masses are additionally characterized as pellets in drug store. Pellets can be set up by numerous strategies, the compaction and medication layering procedures being the most generally utilized today. Despite which producing process is utilized, pellets need to meet the accompanying necessities; [1]

1. They ought to be circular and have a smooth surface; both considered ideal attributes for consequent film covering.
2. The molecule estimate range ought to be as tight as could reasonably be expected. The ideal size of pellets for pharmaceutical utilize is in the vicinity of 600 and 1000 am.
3. The pellets ought to contain however much as could reasonably be expected of the dynamic fixing to keep the span of the last measurements frame inside sensible breaking points.

The upside of various unit items as a controlled-discharge dose shape is accepted to be their conduct in vivo as a result of their worthwhile scattering design in the gastrointestinal tract and their uncommon size attributes. Gastro-intestinal travel time enormously influences the bioavailability of a medication from an orally regulated controlled discharge planning. Once the stomach had discharged, the circles started to travel in groups. It has been accounted for that pellets littler than around 2.4 mm in breadth, are free from the stomach related capacity of the stomach and the end arrangement of the pyloric sphincter to be discharged from the stomach. A greatest pellet width of 1.5 mm has been suggested for an ideal various unit plan plainly demonstrated that the edge measure must be beneath 1 mm. As indicated by there is no real cut-off size for gastric discharging, however as the span of the pellets increment, unsurprising exhausting from the fed stomach winds up plainly dubious and profoundly factor.[1]

Methods of Preparation Pellets[2,3,4]

Compaction and medication layering are the most broadly utilized pelletization systems in pharmaceutical industry. Of the compaction systems, expulsion and Spheronization is the most well known technique. As of late, in any case, liquefy pelletization has been utilized much of the time in making compaction pellets utilizing an alternate sort of hardware, e.g. a high shear blender. Other pelletization techniques, for example, globulation, balling and pressure are likewise utilized as a part of the advancement of pharmaceutical pellets in spite of the fact that in a restricted scale. Following of the for the most part strategies utilized for the pelletization;

Extrusion-Spheronization[3]

Expulsion Spheronization is a various advance compaction process involving dry blending of the fixings with excipients, wet granulation of the mass, expulsion of the wetted mass, charging the extrudates into the Spheronizer to create a circular shape, drying the wet pellets in a dryer and, at last, screening to accomplish the required size dissemination. The granulation step can be performed both in group sort processors, including a traditional planetary blender, and in vertical or even high-shear and sigma-cutting edge blenders, and in consistent blenders, and high-shear twin-screw blender extruder. Extruders for the expulsion procedure (step) have been grouped by and large as screw, strainer and wicker container, roll and slam extruders. In view of the sort of encourage component used to Transport the mass towards the kick the bucket, they have been comprehensively delegated screw, gravity or cylinder sort extruders. Most Spheronizer have been planned in view of a rotating notched plate driven by a variable-speed drive unit at the base of a smooth-walled drum. The drum limit, plate measurement and plate configuration may differ. Keeping in mind the end goal to build the limit of the Spheronization arrange, a persistently working Spheronizer has been presented. The procedure produces items going from scarcely formed, sporadic particles, to exceptionally round particles with radically extraordinary properties. Adjusting the organization, the pulverizing liquid or the procedure conditions, can modify tableting qualities. The principle preferred standpoint of delivering drug-stacked circles or pellets is the ability to create round pellets of a uniform size and high medication content up to 90%. As of late, extraordinary sorts of fluidized bed rotating processors have been created more Effectively to prepare compaction-sort pellets, for example, the expulsion Spheronization process in a one-advance process. This system has tackled numerous issues identified with the multi-step expulsion and Spheronization process.

MATERIALS

Ivabradine Hydrochloride received form Astron Research Center, Ahmedabad as a gift sample. Microcrystalline cellulose, Lactose, PVPK 30, Colloidal Silicone Dioxide, Talc and Triethyl Citrate purchased from S.D. Fine chemicals, Ahmedabad. Methacrylic acid and Kollicoat SR 30 D received from Olcare Laboratory, Mumbai.

METHODS [5, 6, 7]

Pre-formulation study

Organoleptic Characteristics

Colour and odour of Ivabradine Hydrochloride were characterized and recorded using descriptive terminology.

Flow Properties

Bulk density (BD)

Weigh accurately 1 g of drug (M), which was previously passed through 20 # sieve and transferred in 10 ml graduated cylinder. Carefully level the powder without compacting and read the unsettled apparent volume (V_0). Calculate the apparent bulk density in gm/ml by the following formula:

Bulk density = weight of powder / Bulk volume

Tapped density (TD)

Weigh accurately 1 g of drug, which was previously passed through 20 # sieve and transfer in 10 ml graduated cylinder. Then manually tap the cylinder from the fixed height. Tap the cylinder for 100 times and measure the tapped volume (V_1) Calculate the tapped bulk density in gm/ml by the following formula:

Tapped density = weight of powder / Tapped volume

Carr's index

The Compressibility Index of the powder blend was determined by Carr's compressibility index. It is a simple test to evaluate the BD and TD of a powder and the rate at which it packed down. The formula for Carr's Index is as below:

Carr's index (%) = [(TD-BD) x100] / TD

Hausner's ratio

The Hausner's ratio is a number that is correlated to the flow ability of a powder or granular material.

Hausner's ratio = TD / BD

Angle of repose

The angle of repose of API powder was determined by the funnel method. The accurately weight powder blend were taken in the funnel. The height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the powder blend. The powder blend was allowed to flow through the funnel freely on to the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation.

$$\tan \phi = h/r$$

Where, h and r are the height and radius of the powder cone respectively.

Solubility studies

The solubility of the drug in distilled water, 0.1 N HCl and buffer solutions was determined by phase equilibrium method. An excess amount of drug was taken into the 50 ml conical flasks containing 20 ml of distilled water. Conical flasks were closed with aluminium foil and constantly agitated at room temperature for 24 hr, using rotary shaker. After 24 hr, the solution was filtered through filter paper. The amount of drug solubilised was then estimated by spectrophotometrically.

Melting point determination

Melting point determination of the drug sample was done by open capillary method. Drug was taken in glass capillary whose one end was sealed by flame. The capillary

containing drug was dipped in liquid paraffin inside the melting point apparatus. Melting point was the first indication of purity of the sample since the presence of relatively small amount of impurity can be detected by a lowering as well as widening in the melting point range.

Preparation of calibration curve of Ivabradine HCl [8, 9]

Standard solution

Ivabradine hydrochloride, 100 mg was weighed accurately and transferred into the 100 mL standard flask. A small amount of pH.6.8 phosphate buffer was added to dissolve the drug. The volume was made up to 100 mL with buffer.

Working standard solution

From the above standard solution, 10µg/mL concentration was prepared by diluting with pH 6.8 phosphate buffer.

Scanning of absorption maxima

Working standard solution of 10 µg/ml of Ivabradine hydrochloride was scanned in the wavelength range of 200-400 nm against the reagent blank to obtain the absorption maxima using UV-visible Spectrophotometer (Shimadzu).

Construction of calibration curve

Standard solution of Ivabradine hydrochloride was diluted with phosphate buffer to get dilutions containing 10, 20, 30, 40 and 50 µg/ml of Ivabradine hydrochloride. The absorbencies of these diluted solutions were measured using at 286 nm against reagent blank. Each sample was estimated in triplicate, and the average values reported. Same method was followed by using 0.1 N HCl (pH 1.2) as a solvent.

Drug - Excipients compatibility studies

To investigate any possible interactions between the drug and Excipients used, the FT-IR spectra of pure drug and its physical mixture with different Excipients/final formulation mixture were carried out using FTIR spectrophotometer. The samples were prepared as KBr (potassium bromide) disks compressed under a pressure of 150 lbs. The wave number range is selected in between 400-4000 cm^{-1}.

Dose Calculation

The pharmacokinetic parameters of Ivabradine HCl were utilized for the calculation of theoretical drug release profile for 12 hrs dosage form.

The total dose of Ivabradine HCl required for 12 hrs release profile was calculated using following equation**.**

$$\text{Total Dose} = \text{Loading Dose}\{1 + (0.693 \times t/t_{1/2})\}$$

$$= 5\{1 + (0.693 \times 12/2)\}$$

$$= 25.79 \text{ mg} \sim 25.8 \text{ mg}$$

Where,

t is time up to which controlled release is required and t½ is half-life of drug.

Preparation of Pellets

Preparation of drug containing pellets

Extended-release pellets of Ivabradine HCl were prepared by wet granulation technique using Microcrystalline Cellulose and Lactose were passed through the 40 # sieve and mix till uniform mixing obtained. PVPK 30 was passed through 40# sieve and dissolved in a sufficient quantity of purified water using continuous stirring with mechanical stirrer, till thick transparent paste was obtained. Now dry blend was granulated using previously made solution and add extra water if necessary. Above wet mass was transfer in to extruder and collect road shape extrudes. Now above extruded product was transfer in to spheronizer and continuous observed it and collects it after perfect round shape was obtained. It would be taken time for Approximately 10 min. Sprinkle extra talc for reducing clumping formation or reduce the static charges between pellets.

Table 1: Trial batch of Pellets preparation

Material	FUNCTION	A1	A2	A3	A4	A5
Ivabradine HCl	Drug	50 %	50 %	50 %	50 %	50 %
MCC	Spheronizing Agent	22.5 %	10 %	35 %	23.5 %	21.5 %
Lactose	Filler	22.5 %	35 %	10 %	23.5 %	21.5 %
PVP K 30	Binder	5 %	5 %	5 %	3 %	7 %
Water	Vehicle	q.s	q.s	q.s	q.s	q.s
Total		**100 %**	**100 %**	**100 %**	**100 %**	**100 %**

Barrier Coating on Pellets

Prepared pellets were taken for barrier coating in coating machine. 5 % PVPK 30 solution prepared in water and sprayed on pellets up to 1 % weight gain. Coating Parameters are given below table 2.

Polymer Coating

Barrier coated pellets were taken for polymer coating. Polymer coating were done for drug release control. Here Kollicoat SR 30 D was taken as rate controlling polymer. Kollicoat SR 30 D, 30 % ready dispersion taken and diluted with water as per requirement. Talc added as tacking agent

under continuous stirring. At the end triethyl citrate added as plastisizer and stirred for 30 min before use.

Enteric Coating

Polymer coated pellets were taken for barrier coating as per 5.7.3 step.Then finally enteric coating was done on pellets using Eudragit L30D-55 enteric coated polymer up to 5 % weight gain.

Preparation of Coating Solution

First of all, Talc and Aerosil was sifted through 40# sieve. Mixed both excipients and homogenize using water in till very fine particles in solution were obtained. Now collect it and mixed with Eudragit L30D-55 polymer dispersion using mechanical stirrer for the continuous stirring, which help to prevent settlement of talc at the bottom of the mixing tank. Above solution was sifted through the 100 # sieve and used for the coating on the previously prepared pellets.

Enteric Coating of Pellets in Coater

- Pellets were loaded in coating pan.
- Coating of pellets done by using 1.2 mm Nozzle gun.
- Following are the coating parameters;

Table 2: Preliminary Trials for Process Parameters

Preliminary Trials for Die hole size on batch A1	
BATCH	**DIE HOLE SIZE**
D1	0.5 mm
D2	**1.0 mm**
D3	1.5 mm
Preliminary Trials for spheronization speed on batch A1	
S1	600
S2	**1000**
S3	1300
Preliminary Trials for Spheronization time on batch A1	
T1	1 to 5 min
T2	**8 to 12 min**
T3	12 o 18 min
Coating parameters for Barrier coating.	
Parameters	**Value**
Pan	8.5 inch
Gun	1.0 mm
Inlet Air Temp.	40 ° C
Inlet Air Flow	20-40 cfm
Pan rpm	5-8 rpm
Atomization Air Pressure	1.0-1.5 atm
Spray rate	3-5 gm/min

Table 3: Optimization of polymer coating on pellets

Formulation	F1	F2	F3	F4	F5	F6	F7	F8	F9
Ivabradine HCl	50 %	50 %	50 %	50 %	50 %	50 %	50 %	50 %	50 %
MCC	22.5 %	22.5 %	22.5 %	22.5 %	22.5 %	22.5 %	22.5 %	22.5 %	22.5 %
Lactose	22.5 %	22.5 %	22.5 %	22.5 %	22.5 %	22.5 %	22.5 %	22.5 %	22.5 %
PVP K 30	5 %	5 %	5 %	5 %	5 %	5 %	5 %	5 %	5 %
Water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
% Polymer coating	2 %	4 %	6 %	8 %	10 %	12 %	14 %	16 %	20 %

Evaluation of Pellets

Physical Description

Pellets shape observed by visual observation.

Bulk Density

Bulk density = Weight of powder / Volume

Tapped density

Tapped density = Weight of powder / Tapped volume

Carr's index (%)

It is one of the most important parameter to characteristic the nature of powders and granules. It can be calculated from the following equation-

Carr's index = Tapped density - Bulk density / Tapped density X 100

Hausner's ratio

Hausner's ratio is an important character to determine the flow property of powder and granules. This can be calculation by the following formula-

Value < 1.25 indicate good flow (=20% Carr)

While > 1.50 indicate poor flow (=35% Carr)

Hausner's ratio = Tapped density / Bulk density

Drug Content

One hundred milligrams of pellets were dissolved in 100 ml of 6.8 phosphate buffer. The resulting solution was analyzed spectrophotometrically at 301 nm.

In-vitro dissolution profile

Dissolution studies for each formulation were performed in a calibrated 8 station dissolution test apparatus equipped with paddles (USP apparatus II method) employing 900 ml of 1.2 pH 0.1N HCL as a medium for first two hours and in 6.8 pH phosphate buffer for next 2 hours than in 7.4 phosphate buffer as a medium upto 12 hours. The paddles were operated at 50 rpm and the temperature was maintained at 37 ± 0.5 ^{0}C throughout the experiment. Samples were withdrawn at regular intervals up to 12 hours and replaced with equal volume of dissolution medium to maintain the constant volume throughout the experiment. Samples withdrawn at various time intervals were suitably diluted with same dissolution medium and the amount of drug released was estimated by an ultraviolet visible spectrophotometer at 301 nm.

Drug release kinetic study

Data obtained form in vitro drug release studies were fitted to disso calculation software. The kinetic models used are zero order, first order, Korshmers and papps, Hexon crowell, and Higuchi equation.

The rate and mechanism of release were analyzed by fitting the dissolution data into the zero-order equation:

$$Q = k0t$$

Where, Q is the amount of drug released at time t, k0 is the release rate constant. The dissolution data fitted to the first order equation:

$$\ln (100–Q) = \ln 100 – K1\ t$$

Where, k1 is the release rate constant. The dissolution data was fitted to the Higuchi's equation:

$$Q = k2\ t1/2$$

Where, k2 is the diffusion rate constant.

The dissolution data was also fitted to Korsmeyer equation, which is often used to describe the drug release behavior from polymeric systems:

$$\text{Log } (Mt/M\infty) = \log k + n \log t$$

Where Mt is the amount of drug released at time t, M∞ is the amount of drug release after infinite time, K is a release rate constant incorporating structural and geometric characteristics of the tablet, n is the diffusion exponent indicative of the mechanism of drug release.

If n=0.45 the release is Fickian diffusion, if n>0.45 the release is non Fickian diffusion.

Stability studies

Optimized formulation was stored at elevated temperatures such as 40 ^{0}C ± 2 ^{0}C / 75% ± 5 % RH for 30 days. The samples were withdrawn at intervals of 30 days and checked for physical changes as well as drug content and drug release.

RESULTS AND DISCUSSION

Pre-formulation Studies

Characterization of Drug

Table 4: Characteristic Properties of Ivabradine HCl

Sr. No.	Characteristic Properties		Observation/Result
1	Organoleptic Characteristics	***Colour***	White to slightly yellow powder
		Odour	Odorless
2	Flow Properties	***Bulk density (g /ml)***	0.24 ± 0.03
		Tapped density (g /ml)	0.45 ± 0.02
		Carr's index (%)	46.66 ± 0.09
		Hausner's ratio	1.87 ± 0.05
		Angle of repose (ϑ°)	43º ± 2°
3	Melting Point	***By Capillary Method***	196.0 ° C
4	Solubility	***Water***	Soluble (8.5 mg/ml)
		pH 1.2, 0.1 N HCl	Soluble (1.9 mg/ml)
		pH 6.8 Phosphate Buffer	Soluble (7.9 mg/ml)

Based on above physical characterization of API it concluded that the API has a poor flow in nature. Further, Melting point of drug found to be 196.0 °C which was complies with the melting range of the drug from literature. Solubility of drug found satisfactory in water as well as acidic and basic buffer media, hence solubility enhancement is not required.

Optimization of Process Parameters

Optimum Die hole size was needed for proper size of pellets formulation. Machine Provided variable dies hole sizes ranging between 0.5, 1, 1.5 and 2 mm at 0.5 mm (D1) friable small pellets were obtained and at 1.5 mm (D3) big regular shaped pellets were obtained at 1mm (D2) average 1mm spherical pellets were obtained so it was selected for further study.

Table 5: Optimization of Process Parameters

Results of Preliminary Trials for Die hole size		
BATCH	**DIE HOLE SIZE**	**INFERANCE**
D1	0.5 mm	Friable small pellets
D2	**1.0 mm**	**Average 1mm spherical pellets**
D3	1.5 mm	Big regular shaped pellets
Result of Preliminary Trials of Spheronization speed		
S1	600	Long extrudates
S2	**1000**	**Spherical pellets**
S3	1300	Broken particles
Results of Preliminary Trials for Spheronization Time		
T1	1 to 5 min	Extrudates
T2	**8 to 12 min**	**Pellets**
T3	12 to 18 min	Broken pellets

Spheronization speed was optimized for proper spherical shape of pellets formation. Variable spheronization speed was available between 600-1800 rpm available. At 600 rpm (S1) long extrudates were obtained and at 1200rpm (S3) pellets were broken. At 1000rpm (S2) spherical shape pellets were obtained so it was selected for further pellet preparation. Spheronization time is optimized for proper shape of pellets at 1 to 5 minutes (T1) Extrudates were obtained and at 15 to 20 minutes (T3) pellets was broken at a 8 to 12 minutes (T2) spherical shape pellets were obtained so it was further study for pellet formation.

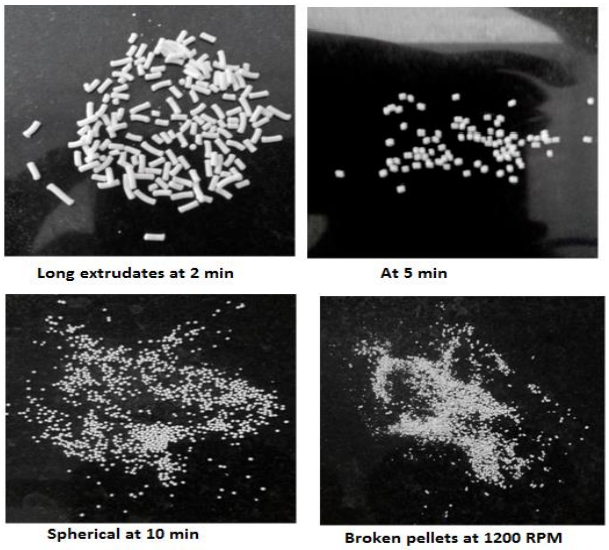

Figure 1: Spherical pellet parameter optimization

Evaluation of Pellets

Micromeritic Properties of Pellets

Evaluations of enteric coated pellets were carried out for flow properties. The flow properties of pellets were most important parameter for filling pellets into the capsule shell. The angle of repose values ranges from. 21.65 ± 0.30 to 24.73 ± 0.34 the bulk density and tapped density ranges from 0.72 ± 0.005 to 0.82 ± 0.004 (gm/cm^3) and 0.78 ± 0.003 to 0.90 ± 0.006 (gm/cm^3) respectively. The values of angle of repose, Carr's index and Hausnar's ratio indicate excellent flow properties of pellets. Formulation F1-F9 evaluated for their flow properties and data recorded in below table 6. From the results it concluded that all the formulation having good flow properties. Further it will help during pellets filling if any.

Table 6: Micromeritic Properties of Pellets

Batch	Angle of repose (θ)	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's ratio
F1	23.43±0.42	0.80±0.004	0.85±0.003	4.86±0.15	1.05±0.001
F2	21.13±0.28	0.74±0.004	0.78±0.003	4.98±0.27	1.04±0.001
F3	22.97±1.09	0.82±0.004	0.85±0.002	2.82±0.69	1.02±0.003
F4	24.73±0.34	0.81±0.004	0.90±0.006	9.12±0.42	1.10±0.004
F5	22.39±0.56	0.82±0.004	0.87±0.009	4.80±0.72	1.05±0.006
F6	21.65±0.30	0.78±0.009	0.88±0.001	5.81±0.49	1.06±0.005
F7	22.19±0.31	0.74±0.003	0.86±0.004	12.95±0.47	1.14±0.004
F8	21.69±0.30	0.72±0.005	0.80±0.007	09.01±0.42	1.10±0.004
F9	22.13±0.28	0.75±0.003	0.83±0.004	8.93±0.32	1.09±0.203

Evaluation of Pellets for Drug Content

Formulation F1-F9 checked for Drug Content and results recorded in below table 6.5. All formulations were found within the limit. It means drug was distributed equally in properly in the formulation.

Evaluation of Pellets for Drug Release Study

Drug release study of enteric coated pellets carried out in 0.1 N HCL for first 2 hours. In first 2 hours it seen that the enteric coating was sufficient to remain stable in acidic pH. No drug release observed from F1-F9 in first 2 hr in all formulation. So it can concluded that the 5 % Eudragit

L30D-55 Enteric coating was sufficient to prevent the drug loaded sustained release pellets from acidic pH. Further when the pellets were checked in alkaline pH after 2 hr the drug release was started. Here Kollicoat SR 30 D was taken to control the drug release. From 3 hr onwards we can see the drug release in pellets. F1 gives maximum 54 % drug release in four hour. Further the % of polymer coating increase in F1 to F9 side, % drug release is decrease in 4 hour. So enteric coat was break in alkaline pH. F1-F9 shows drug release more than 10 % in 3 rd hours. Also release was continuing in 4 th hours. And more than 20 % drug release after 4 hour. One more important thing is that bursting effect was not seen in any formulation. Further the effect of Kollicoat SR 30 D seen in formulation. 2 % coating F1 batch release drug in 9 hr. F2 gives up to 10 hours and F3 gives up to 11 hours and increase in % Coating should retard the drug release. F6 batch which have 12 % polymer coating release 99.9 % drug release in 12 hr. this is the batch into which our objectives achieved. Further more than 12 % polymer coating batch release less than 95 % drug in 12 hr. F7-F9 batch in which amount of polymer coating is more than 12 % retard the drug release and no achieved up to 90 % in 12 hour. So we can conclude that the 12 % polymer coating was sufficient to release the drug up to 12 hours.

Table 7: % Drug release of F1-F9

Time (Hr)	F1	F2	F3	F4	F5	F6	F7	F 8	F9
1	0	0	0	0	0	**0**	0	0	0
2	1.05	1.45	0.98	1.32	2.03	**1.06**	0.89	2.15	1.87
3	35.40	25.10	21.78	23.97	11.90	**13.58**	18.74	14.78	10.40
4	54.60	34.90	31.41	27.69	21.63	**25.51**	33.59	20.40	18.60
5	69.70	55.90	42.98	31.81	35.24	**38.87**	43.94	25.54	26.90
6	81.40	68.41	51.87	41.71	42.67	**48.98**	48.81	30.83	28.40
7	89.90	75.60	65.90	47.01	48.81	**56.58**	54.40	35.08	32.50
8	94.50	86.40	75.80	53.47	52.89	**64.10**	59.66	44.98	42.90
9	99.90	91.60	85.90	62.00	57.66	**72.60**	61.40	48.94	52.60
10	99.90	95.80	90.40	78.34	63.79	**80.90**	73.29	55.07	60.40
11	99.90	99.80	99.80	86.53	73.35	**83.80**	88.48	62.21	71.80
12	99.90	99.90	99.90	93.60	92.13	**99.80**	94.50	88.60	84.60

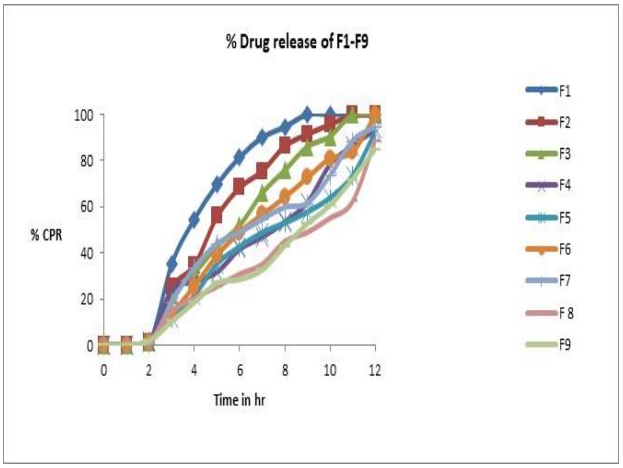

Figure 2: % Drug release of F1-F9

CONCLUSION

In the present study, a novel extrusion-spheronization method employed to prepare pellets of Ivabradine HCl using various carrier materials to load the drug into pellets. Microcrystalline cellulose incorporated in formulation via extruder-spheronization to enhance the rheological properties of the wetted mass, resulted in good sphericity, low friability, high density, and smooth surface for successful extrusion and spheronization. Pellets are prepared using extrusion-spheronization and the process parameters are optimized. 1.0 mm die hole size, 1000 rpm spheronization speed and 8-12 min spheronization time was optimized for further study in core pellets. Polymer coating done with Kollicoat SR 30 D as rate controlling polymer and finally enteric coating done with Eudragit L30D-55.Prepared enteric coated pellets were checked for flow properties. It found that all formulation has a Hausner's ratio below 1.2, so all formulation has good flow properties. Formulation F1-F9 passed the friability test, so mechanical strength was also good in all batches of enteric coated pellets. Drug content found within limit. Drug distributed properly in all batches.Drug release in formulation F1-F9 studied and it found that the low polymer concentration (2 %) was unable to retard the drug release up to 12 hr so concentration increased batch by batch and finally 12 % coating batch gives desired results which retard the drug release up to 12 hr. also found that the drug release was very low after more % coating than the 12 %. Hence based on that the F5 batch was optimized batch and its found stable during stability study of 1 month.

Acknowledgment: The Author and co-author, thanks to Saraswati Institute of Pharmaceutical Sciences, for providing the necessary facility to accomplish the work we

also humble gratitude to our colleague and non-teaching staff for their support during the work.

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Source of Support: The author(s) received no financial support for the research, authorship, and/or publication of this article.

Conflict of Interest: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.