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FORMULATION AND EVALUATION OF BILAYER FLOATING TABLETS OF ATORVASTATIN AND CAPTOPRIL

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Keywords:

Atorvastatin, Bilayer, Captopril, Carnauba wax, Cetyl alcohol, HPMC, PEG and Sustained-release

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ABSTRACT: The aim of the present research work was to develop a bilayer floating dosage form of immediate-release Atorvastatin (ATR) and sustained release Captopril (CPT) in matrix form for the treatment of hyperlipidaemia and hypertension to reduce multiple dosing frequencies and enhance patient compliance. ATR belongs to the BCS Class II category having poor aqueous solubility, which was enhanced by using hydrophilic polymer PEG 8000 by kneading technique. A sustained layer of CPT was prepared by melt granulation technique using various concentrations of carnauba wax with HPMC K 100 M and Carbopol 934 P. All the parameters before and after compression were evaluated. ATR-PEG ratio of 1:0.25 showed a higher drug release of about 97.42% within 60 min. The optimized CPT sustained layer SR2 shown the highest drug release 98.2% in 12 h. *In-vitro* drug release studies carried out as per USP in pH 1.2 buffer using type II apparatus. The CPT layer exhibited release kinetics in the first order and followed the diffusion and erosion mechanism. The FTIR, XRD studies, and SEM analysis indicated the absence of strong interaction between drug and polymer and compatibility among them. The novel concept of Bi-layer gastric floating can be utilized for the formulation of ATR and sustained release of CPT with a floating period of >12 h and 45 s lag time.

INTRODUCTION: Cardiovascular diseases are largely non-communicable diseases resulting in the death of millions of people, of which more than 75% were in low income and middle-income groups. A report on heart failure from 1971 concluded that hypertension was the dominant cause of heart failure [1]. To reduce the global burden of cardiovascular disease, WHO members decided to give counseling and drug treatment for at least 50% of eligible people by 2025 [2].

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Oral route of drug delivery has the wide acceptance of 50-60% of total dosage forms, and it is the most convenient and preferred route to achieve the systemic effect due to its ease of administration, pain avoidance, patient compliance, and flexibility in formulation [3]. Hypertension is a dynamic cardiovascular disorder. It mainly occurs due to chronic elevation of systemic arterial pressure above the threshold value of approximately 115/75 mm Hg [4].

Progression is associated with structural and functional cardiac and vascular abnormalities that damage the heart, kidneys, brain, Vasculature, and other organs and lead to death [5]. Hyper-lipidaemia is a state of abundance, greasy substances called lipids, generally cholesterol and triglycerides, in the blood.

It is likewise called hyperlipoproteinemia in light of the fact that these overabundance lipids travel in the blood connected to proteins. These greasy components can stay as dissolved minute particles while available for use in circulation in this way only.

Hyperlipidaemia is a significant reason for atherosclerosis and atherosclerosis-related conditions like coronary heart disease (CHD), ischemic cerebrovascular ailment, peripheral vascular disease, and pancreatitis [6].

Floating systems are low-density systems that have adequate buoyancy to float over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying rate for a long period of time. The drug is released slowly at the desired rate from the system while the system is floating on the gastric contents.

The residual system is emptied from the stomach after the drug release. This results in increased gastric residence time and better control of the fluctuation in plasma drug concentration [7].

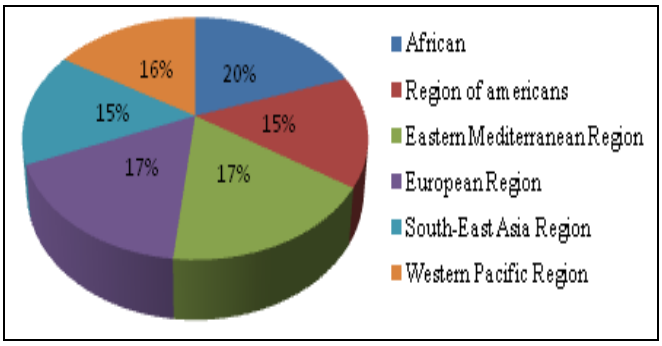

FIG. 1: PREVALENCE OF CARDIOVASCULAR DISEASE

Solid dispersion technology has received greater prevalence because of its capacity to increase the solubility of poorly soluble drugs [8-10]. The most significant attribute of solid dispersion technology is that the medication ought to be exceptionally dispersed in appropriate carriers [11]. Atorvastatin owing to its low dissolvability the oral bioavailability is just around 14% and had the impact of the first-pass metabolism.

There is no statistically noteworthy differences found in any of the lipid values estimated between the morning and night administration of atorvastatin [12]. Therefore, the development of formulation with ATR is challenging to the formulator requiring solubility enhancement through solid dispersion technique [13]. The aim of the work was to develop and evaluate an oral pharmaceutical equivalent, a stable, robust, and controlled bilayer tablet of Atorvastatin and Captopril, which is very well tolerated, having less side effects with improved bioavailability and high patient acceptance.

MATERIALS AND METHOD:

Materials: Atorvastatin (ATR), PEG8000, Crospovidone, Croscarmellose sodium, Sodium starch glycolate, HPMC K100M, and Carbopol 934P were purchased from Yarrow Chem. Products, Mumbai. Captopril (CPT) was received as a gift sample from Adcock Ingram, Bangalore. Carnauba wax, Cetyl alcohol, Talc, Magnesium stearate was received from Ottokemi. Lactose, Sodium bicarbonate and Citric acid were purchased from Finar Ltd. Methanol from Sd- fine chemicals and HCl from Fisher scientific were received.

Method:

Formulation and Design of Bilayer Floating Tablets:

Solubility Enhancement of Atorvastatin: ATR is a BCS class II drug having low solubility and high permeability requiring solubility enhancement. Solid dispersion technique used for this purpose.

Preparation of Solid Dispersion: The solid dispersions were prepared by using 2 methods such as physical mixture, kneading method by using two different carriers (PEG 8000 and HP-β-Cyclodextrin).

The drug: carrier were used in the ratio of 1:0.25, 1:0.5, 1:0.75, 1:1 as shown in **Table 1**. The physical mixture was prepared by taking the carrier and the drug in the mortar and pestle, triturating for 15 min. The sample was sieved through 60#.

In the case of kneading method, polymer in different ratios is added to the mortar and triturated with a small quantity of ethanol to prepare a slurry. The drug is incorporated into the slurry slowly with constant trituration.

The prepared slurry is then air-dried at 25 °C for 24 h. The resultant product is pulverized and passed through 80# and stored in desiccator over fused calcium chloride [14].

TABLE 1: SOLUBILITY ENHANCEMENT OF ATR USING HP-B CYCLODEXTRIN AND PEG 8000

Formulation code	Carrier	Drug: Carrier ratio	Method
SD1	HP-β Cyclodextrin	1:0.25	Physical mixture
SD2		1:0.5	
SD3		1:0.75	
SD4		1:1	
SD5		1:0.25	Kneading method
SD6		1:0.5	
SD7		1:0.75	
SD8		1:1	
SD9	PEG 8000	1:0.25	Physical mixture
SD10		1:0.5	
SD11		1:0.75	
SD12		1:1	
SD13		1:0.25	Kneading method
SD14		1:0.5	
SD15		1:0.75	
SD16		1:1	

Formulation of Atorvastatin Immediate Release Layer: Based on the physicochemical characterization and evaluation parameters, the solid dispersions containing 1:0.25 ratio drug: carrier (PEG 8000) prepared by kneading method was optimized for immediate release tablet, and further experimentation had been carried out with this formulation only.

Accurately weighed quantity of all the excipients required for the formulation of immediate-release layer was taken in mortar and pestle and mixed uniformly. The active ingredient was added slowly and mixed thoroughly for about 30 min.

The powder was passed through 60# and transferred to a polythene bag. Finally, talc and magnesium stearate were added and mixed for 5 min. The composition details are shown in **Table 2**. The powder blend was compressed by direct compression using an 8mm round punch set on Karnavati make eight station tablet compression machine.

TABLE 2: FORMULATION OF ATORVASTATIN IMMEDIATE RELEASE LAYER

Contents (mg)	Formulation Code		
	IF1	IF2	IF3
Atorvastatin	10	10	10
PEG 8000	2.5	2.5	2.5
Sodium starch glycolate	4	-	-
Crospovidone	-	4	-
Croscarmallose sodium	-	-	4
Magnesium stearate	3	3	3
Talc	2	2	2
Lactose	78.5	78.5	78.5
Total	100	100	100

Formulation of Sustained Release Floating Layer of Captopril: The sustained release layers were prepared by the melt granulation technique. The hydrophobic polymers required for retarding the drug release (carnauba wax, cetyl alcohol) were taken in a crucible and melted at a temperature of 60 ºC. The drug was added slowly with constant stirring until a uniform mixture was formed and allowed to cool at room temperature. The sample was scrapped and triturated in mortar and pestle to get a fine powder.

TABLE 3: FORMULATION OF SUSTAINED RELEASE LAYER BY MELT GRANULATION TECHNIQUE

Contents (mg)	Formulation code							
	SR1	SR2	SR3	SR4	SR5	SR6	SR7	SR8
Captopril	25	25	25	25	25	25	25	25
Carnauba wax	25	50	100	150	-	-	-	-
Cetyl alcohol	-	-	-	-	25	50	100	150
HPMC K 100M	150	150	150	150	150	150	150	150
Carbopol 934 P	50	50	50	50	50	50	50	50
Sodium bicarbonate	20	20	20	20	20	20	20	20
Citric acid	20	20	20	20	20	20	20	20
Talc	2	2	2	2	2	2	2	2
Magnesium stearate	3	3	3	3	3	3	3	3
Total	295	320	370	420	295	320	370	420

The required other excipients were triturated for about 15 min, passed through 60#, and transferred to a polyethylene bag. The polymers HPMC and Carbopol were used in fixed concentration based on results of previous experimentation, experience and also based on literature. Finally, talc and magnesium stearate were added and blended for a few min. The composition particulars are shown in **Table 3**. The blend was compressed using 10 mm punch set using Karnavati 8 station compression machine.

Evaluation Parameters:

Precompression Study:

FTIR Spectroscopy: Physicochemical interaction of drug and polymer were conducted by FTIR spectroscopy using a diamond disc method at 400-4000 cm-[1 15]. The FTIR studies were also carried out for pure drug, solid dispersion, polymers, ATR powder mixture, CPT powder mixture, and mixture of both formulations.

Differential Scanning Calorimetry: Differential scanning calorimetry of the pure drugs and drug-loaded bilayer tablets were carried out simult-aneously with DSC analyzer. An amount 4 - 5 mg of the crushed bilayer tablet placed in aluminum pans and sealed prior to the test. Measurement was performed at a rate 20 ºC /min under a nitrogen flow of 25 ml/min over a temperature range of 25 to 180 ºC. Indium was used for the calibration of the equipment. The variation in the peaks helps to determine the interaction between the drug and the excipients. It helps in the selection of suitable excipients [16-17]. The DSC studies were also carried out for pure drugs, polymers, solid dispersion atorvastatin tablet mixture, captopril layer mixture, and mixture of both the layers.

X-Ray Powder Diffraction: X-Ray powder diffraction (XRPD) is utilized to identify amorphous and polymorphic forms of a substance, while the sharper peaks in the image indicate a more crystalline material. The intensity of radiation is recorded. The X-ray diffraction is unique to a specific substance [18]. The XRD was carried out for ATR, solid dispersion, and immediate release layer.

Scanning Electron Microscopy: Scanning electron microscope (SEM) allows viewing surface analysis of solid dispersions as well as spatial pattern formation for the scanned object. This is very important for the qualitative assessment of their properties, such as particle size, shape, and morphology.

The information obtained may be helpful when confirming the crystal structure of the analyzed sample [19]. SEM was carried out for ATR, solid dispersion, and the immediate release layer.

Evaluation of Pre-compression Parameters: Prior to the compression into tablets, powders were evaluated for properties like bulk density, tapped density, powder flow properties like Angle of repose, Carr's index and Hausner's ratio [20-21].

Angle of Repose (θ): The angle of repose was then calculated using the formula,

$$\text{Tan } \theta = h / r$$

Where, θ = Angle of repose, h = height of pile, r = radius of the base of the pile.

Bulk Density (Db): It is the ratio of powder to bulk volume. Bulk density is expressed in gm/cc and is given by,

$$\text{Bulk density} = (\text{Mass}) / (\text{Bulk volume})$$

Where, Db = Bulk density (gm/cc), M is the mass of powder (g) Vo is the bulk volume of powder (cc)

Tapped density (Dt): It is expressed in gm/cc and is given by,

$$\text{Tapped density} = \text{Mass} / (\text{Tapped volume})$$

Where, Dt = Tapped density (gm/cc) M is the mass of powder (g) Vt is the tapped volume of powder (cc) M is the mass of powder (g) Vt is the tapped volume of powder (cc)

Carr's Compressibility Index: The compressibility of the powder was determined by Carr's compressibility index. Calculated by using the formula:

$$CI = (\text{Tapped density} - \text{Bulk density}) / (\text{Tapped density}) \times 100$$

Hausner's Ratio: It is the ratio of tapped density to the bulk density of the given powder, given by the formula

$$\text{Hausners ratio} = (\text{Tapped density}) / (\text{Bulk density})$$

Charecterization of Solid Dispersions: It was characterized by the percentage of drug yield obtained by solid dispersion, drug content, and *in-vitro* dissolution studies [22].

% Yield of Drug: It was calculated by considering the weight of powder before formulation minus weight of powder after the preparation of dispersion.

$$\% \text{ Yield} = \text{Final weight} / \text{Initial weight} \times 100$$

Drug Content: The drug content was determined by taking solid dispersion equal to 100 mg of the drug and was dissolved in 0.1 N HCl. The sample was sonicated, filtered and analyzed by UV-Visible Spectrophotometer at 235 nm. Amount of the drug present in the solid dispersion was assessed.

***In-vitro* Dissolution Studies:** Dissolution studies were performed for the solid dispersions using the USP dissolution type II apparatus (paddle method) with 75 rpm in 900 ml of 1.2 acidic pH buffer as dissolution medium at 37 ± 0.5 °C.

The samples were withdrawn at predetermined time intervals of 5, 10, 15, 30, 45, and 60 min, and the same amount of preheated (37 ± 0.5 °C) fresh medium was added to maintain sink condition. The percentage of drug release values obtained from the dissolution studies were plotted against time in min.

Post-Compression Parameters Evaluation: Drug content: Ten tablets were selected randomly, weighed, and triturated. A quantity of triturating is equal to 100 mg of the drug. The drug was transferred to a 100 ml volumetric flask and was dissolved in 0.1N HCl. It was sonicated for 30 min and filtered through a 0.45 µm membrane filter. The absorbance after suitable dilutions were measured on a UV Visible Spectrophotometer using 0.1N HCl as blank [23].

Buoyancy / Floating Test: The *in-vitro* buoyancy was determined by floating lag time. Here, the tablets were placed in a 100 ml beaker containing 0.1N HCl. The time required for the tablet to rise to the surface and float was determined as floating lag time, and the total duration of time by which the dosage form remains buoyant is called Total Floating Time (TFT) [24].

***In-vitro* Drug Release and Duration of Floating:** This is determined by using the USP II apparatus (paddle) stirring at a speed of 50 rpm at 37 ± 0.2 °C in simulated gastric fluid (pH 1.2). Aliquots of the samples are collected and analyzed for the drug content. The sample was analyzed by UV-Visible spectrometry. The same amount of buffer was added to maintain the constant volume [25].

Kinetic Analysis of *In-vitro* Drug Release: The kinetic model had described the drug dissolution from a solid dosage form where the dissolved amount of drug is a function of analyzed test time. In order to determine the precise mechanism of drug release from the prepared bilayer floating tablet, drug release data was analyzed according to Zero-order, First order, Higuchi square root, and Korsmeyer-peppas model. The criteria for selecting the most suitable model were chosen on the basis of the best fit of tested result data [26-27].

RESULTS AND DISCUSSION:

Pre-compression Evaluation:

FTIR Spectroscopy Studies: Identification of ATR and CPT were done as per specification. The FTIR studies proved physical and chemical compatibility between drug and polymer, as shown in **Fig. 2** and **Fig. 3.** FTIR spectrum of pure drug ATR showed peaks at 3363 cm^{-1} (O-H- stretching vibration), 3372 cm^{-1} (N-H- stretching vibration), 3226 cm^{-1} (O-H- asymmetric, symmetric vibration), 2886 cm^{-1} (C-H- stretching), 1649- 1578 cm^{-1} (C=O- asymmetric vibration), 1522-1466 cm^{-1} (C-C - stretching), 1317 cm^{-1} (-CH3, -CH2 deformation), 1241, 1215, 1258 cm^{-1} (C-N stretching), 1159, 1176 cm^{-1} (C=O stretching).The solubility enhancement of ATR needs some interaction with the PEG 8000. C-N of ATR interacts with the C-N of PEG 8000.

A slight shift in the C-N stretching vibration of ATR (1241- 1243 cm^{-1}) and disappearance of the C-H stretching vibration of PEG 8000 indicates the interaction between ATR and PEG 8000. There is no incompatibility, and the powder blend can be formulated into immediate release tablet, also shown in **Fig. 4** and **Fig. 5.**

The sustained release mixture consists of CPT along with Carnauba wax, HPMC K100M, Carbopol 934P. The HPMC K100M has shown

characteristic peaks at 3449-3423 cm^{-1} (OH vibration), 2900 cm^{-1} (hydroxyl-propyl stretching vibration), 1654 cm^{-1} (OH stretching vibration and intramolecular bonding), 1518-1459 cm^{-1} (methoxy asymmetric bending), 1397- 1375 cm^{-1} (Methoxy symmetric bending vibration) shown in **Fig. 6** and **Fig. 7.**

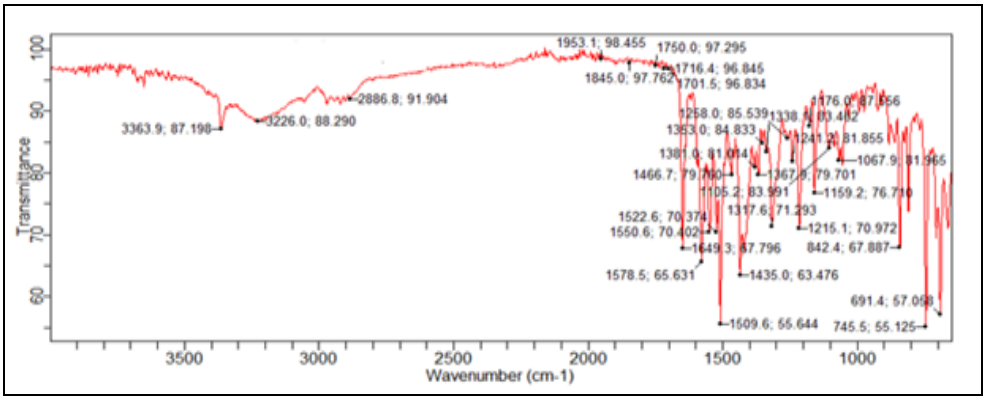

FIG. 2: FTIR SPECTRUM OF ATR

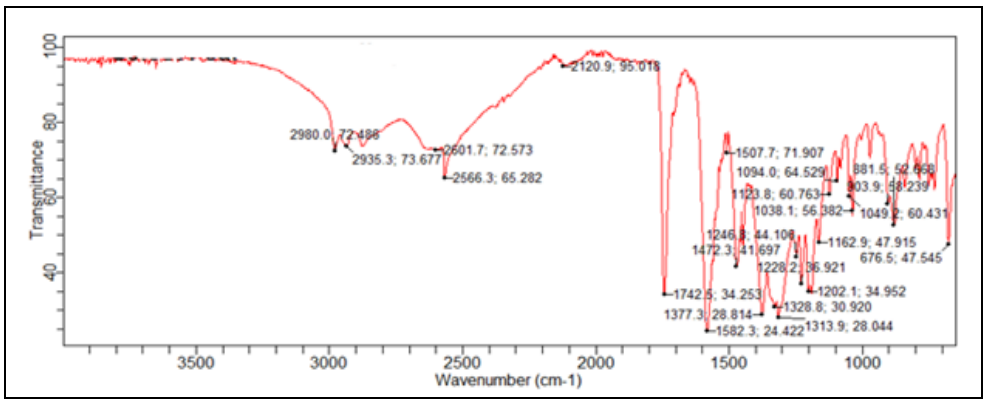

FIG. 3: FTIR SPECTRUM OF CPT

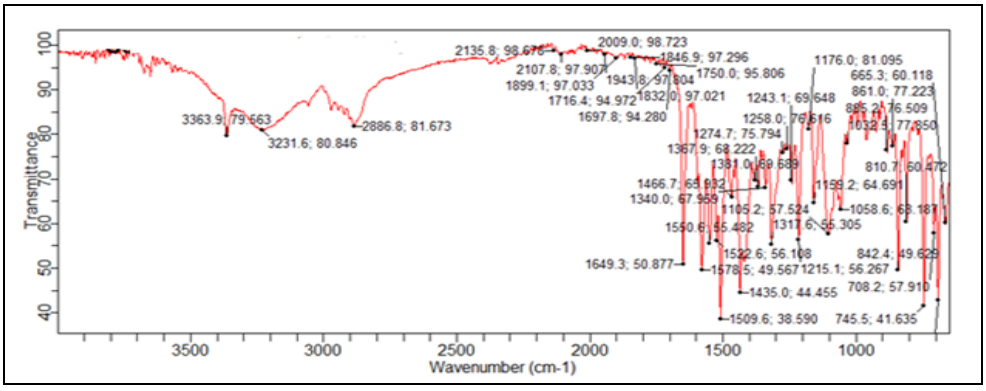

FIG. 4: FTIR-SPECTRUM OF PURE DRUG AND PEG 8000

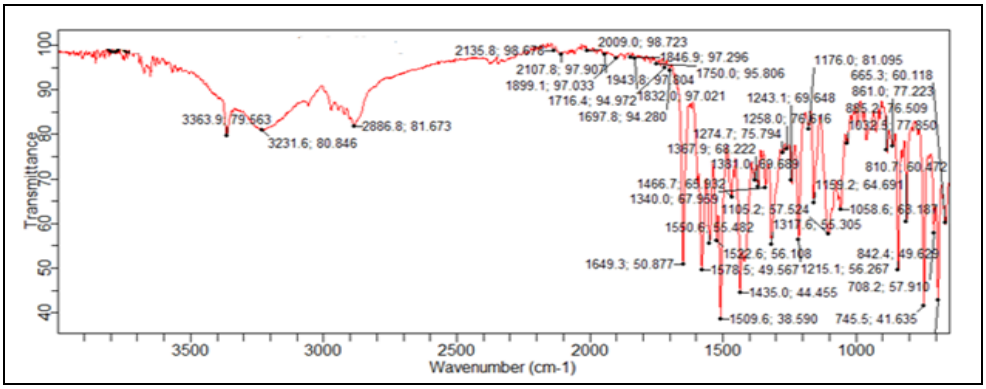

FIG. 5: FTIR SPECTRUM OF IMMEDIATE RELEASE ATR POWDER BLEND

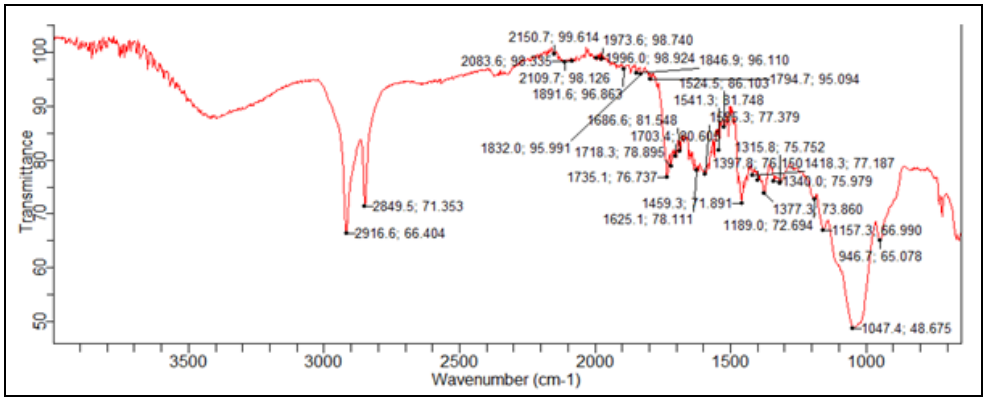

FIG. 6: FTIR SPECTRUM OF SUSTAINED RELEASE CPT TABLET

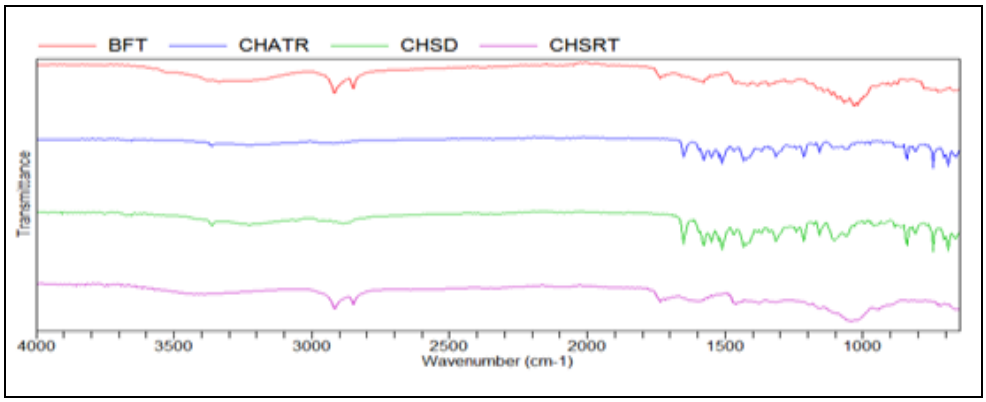

FIG. 7: FTIR SPECTRUM OF OPTIMIZED BFT FORMULATION

DSC Studies: The melting point of ATR and CPT was carried out by using the capillary method and DSC studies.

ATR showed a sharp endothermic peak at 160 °C, and Captopril showed an endothermic peak at 110 °C, and in the capillary method, the melting point was found to be for ATR at 162 °C and for captopril at 108 °C shown in **Fig. 8** and **Fig. 9** that complies with the standard value in the official monograph as per IP.

DSC thermogram of ATR showed a sharp endothermic peak at 160 °C. DSC thermogram of PEG 8000 showed a sharp endothermic peak at 60 °C. The thermogram had not shown any extra peaks, which indicates that there is no incompatibility between the drug and the polymer **Fig. 10**.

The thermogram had not showed any extra peaks, which indicate existence of no incompatibility between the drug and the polymer.

There was a slight shift in the endothermic peak of the pure drug in case of immediate-release tablet **Fig. 11,** which is not a significant change, and drug is compatible with the powder blend. DSC thermogram of optimized bilayer floating tablet was shown in **Fig. 12**

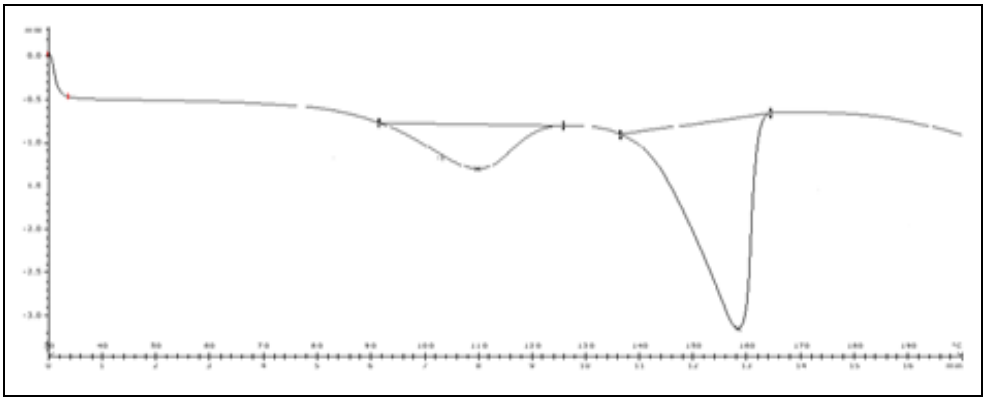

FIG. 8: DSC THERMOGRAM OF ATR

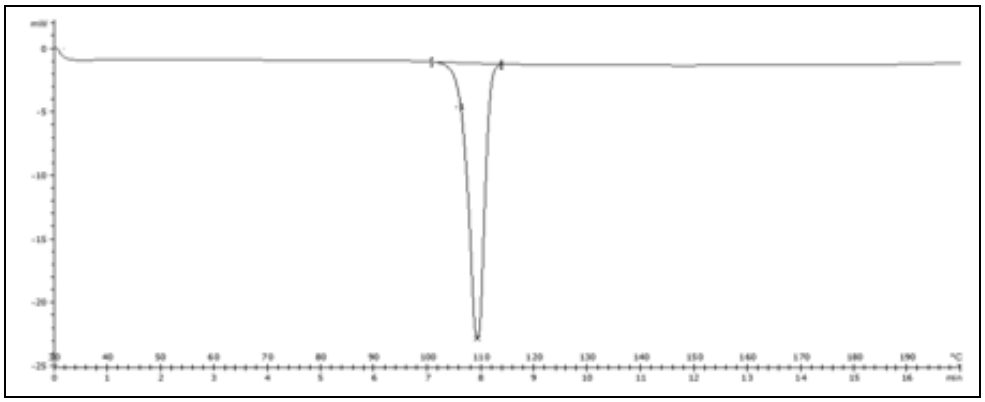

FIG. 9: DSC THERMOGRAM OF CPT

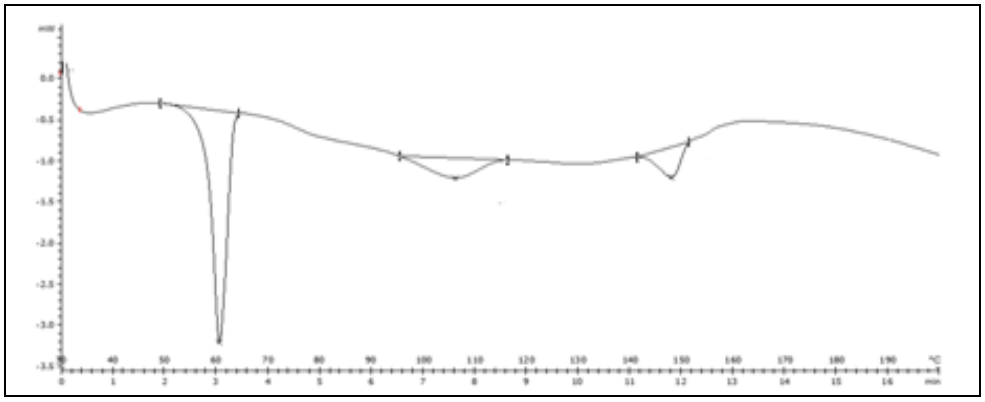

FIG. 10: DSC THERMOGRAM OF SOLID DISPERSION (ATR+ PEG 8000)

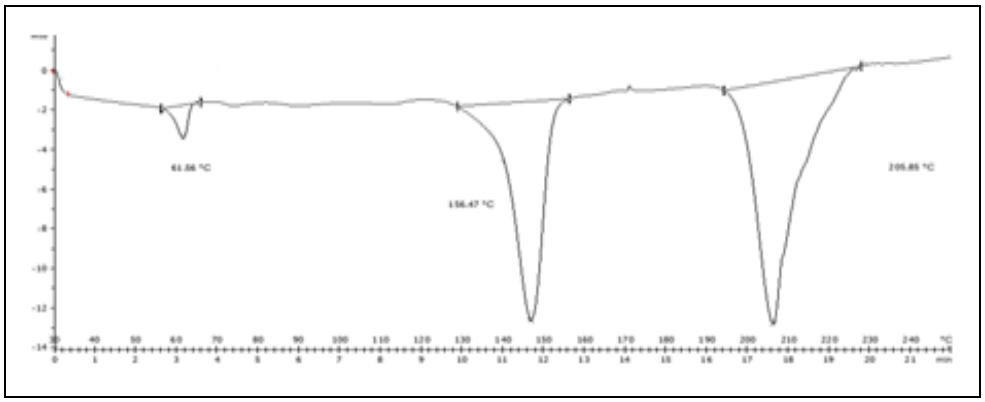

FIG. 11: DSC-SPECTRUM THERMOGRAM OF IMMEDIATE RELEASE ATR POWDER BLEND

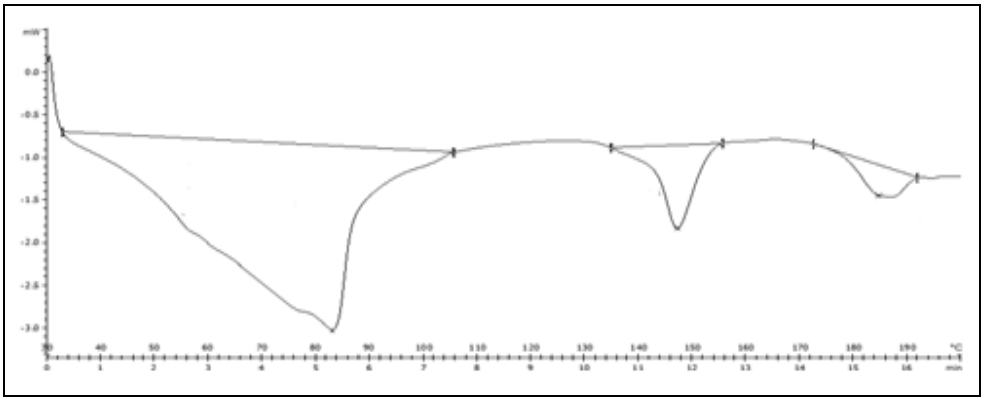

FIG. 12: DSC THERMOGRAM OF OPTIMIZED BILAYER FLOATING TABLET

XRD Studies: XRD pattern of ATR pure drug and SD was depicted in **Fig. 13** and **Fig. 14.** The XRD pattern showed the diffractogram at 2^{θ} equivalent to 5.89^{o}, 22.46^{o}, 26.72^{o}, 30.89^{o} and 32.98^{o}. This

signifies the crystal nature of ATR. The XRD of SD showed less intense peak at 2^{θ} equivalent to 21.56^{o}, 24.87^{o}, 27.58^{o}, 30.89^{o} due to partial transition of ATR from crystalline to amorphous form. The diffract gram of ATR was disappeared. The conversion of crystalline to amorphous form indicates the enhancement of the solubility of ATR. The diffractogram IRT powder blend a showed a less intense peak at 2^{θ} equivalent to 21.56 ^{o}, 24.87 ^{o}, 27.58 ^{o}, 30.89^{o}. The same peaks were observed in case of solid dispersion, which indicates that the amorphous form of the solid dispersion was retained during the formulation of immediate-release powder blend **Fig. 15**.

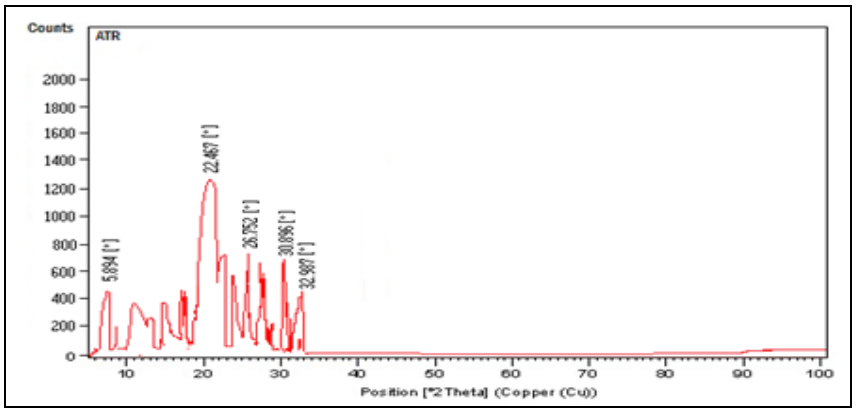

FIG. 13: XRD PATTERN OF ATR

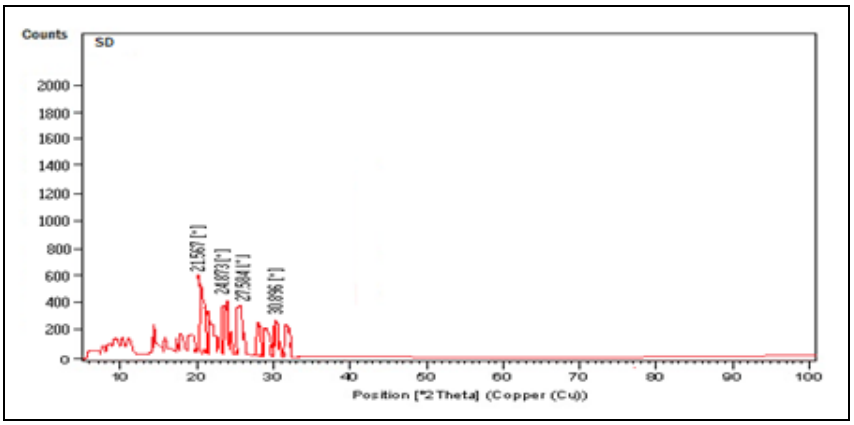

FIG. 14: OPTIMIZED SD-XRD PATTERN

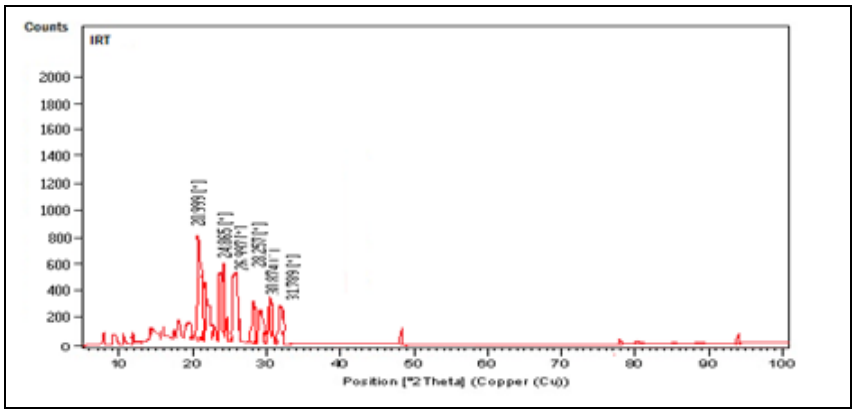

FIG. 15: IMMEDIATE RELEASE POWDER BLEND - XRD SPECTRUM

SEM Studies: The photograph of ATR in **Fig. 16** reveals that the drug was crystalline in nature. The SEM of SD did not show any crystalline ATR on the surface of the formulation. This indicates that the drug and carrier are mixed homogeneously due to the absence of the crystalline nature of ART in the SD shown in **Fig. 17**. This indicated the presence of amorphous ATR in the formulations. The micro-photography of ATR revealed that the crystalline nature of the drug was converted to amorphous form when compared with the ATR, as shown in **Fig. 18.**

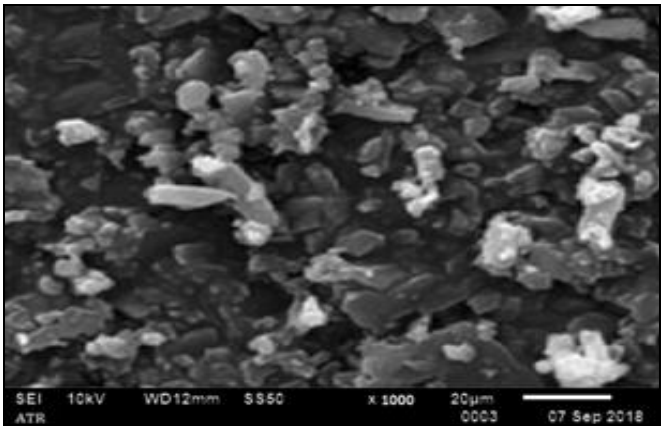

FIG. 16: SEM ANALYSIS OF ATR

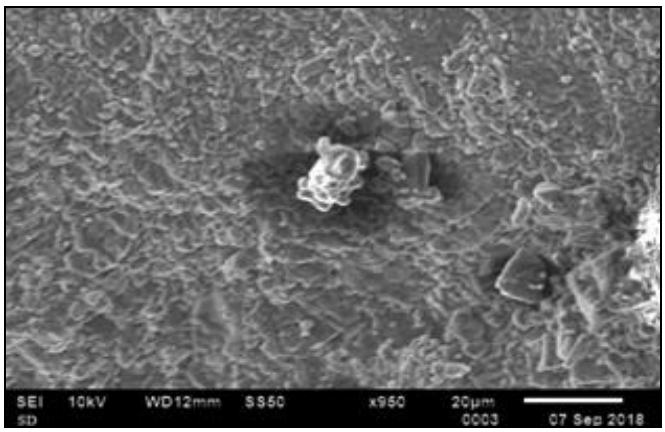

FIG. 17: SEM ANALYSIS OF OPTIMIZED SD

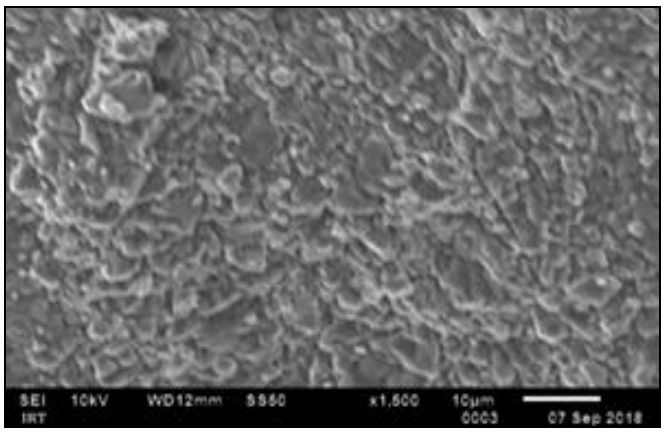

FIG. 18: SEM SPECTRUM OF IMMEDIATE RELEASE POWDER BLEND

Pre-compression Evaluation: The measured values of angle of repose, bulk density and tapped density and Carr's index and Hausner's ratio and prepared each formula powder mixture of immediate release and sustained release are illustrated in **Table 4** and **Table 5.**

The angle of repose for all the immediate release formulations fell within the range of 24.51-27.40° indicating good to acceptable flow properties when compared to a pure drug whose angle of repose was found to be 33.66°.

Compressibility index for all formulations was found to be in the range of 13.7% to 17.02% showing excellent flow properties to that of the pure drug. Hausner's ratio was found to be 1.16 to 1.31 showed good flow properties in relation with compressibility index values less than 1.25 indicate good flow (=20% compressibility index), greater than 1.25 poor flow (=33% compressibility index).

The angle of repose for all the sustained release formulations fell within the range of 20-21° indicating good to acceptable flow properties. The compressibility index for all formulations was found to be in the range of 16.12% to 26.19% showing good to excellent flow properties.

Hausner's ratio was found to be 1.19 to 1.35 showed good flow properties in relation with compressibility index values less than 1.25 indicate good flow (=20% compressibility index), greater than 1.25 poor flow (=33% compressibility index).

TABLE 4: MICROMERITIC PROPERTIES OF PURE DRUG AND ATR IMMEDIATE RELEASE FORMULATIONS

Formulation Code	Angle of Repose*(θ)	Bulk Density* (g/cm^3)	Tapped Density* (g/cm^3)	Compressibility Index* (%)	Hausner's Ratio*
ATR	33.66 ± 0.73	0.52 ± 0.94	0.67 ± 1.02	22.38 ± 0.68	1.48 ± 0.36
IF1	26.11 ± 0.91	0.43 ± 0.81	0.50 ± 0.94	14.00 ± 0.79	1.16 ± 0.92
IF2	27.40 ± 0.85	0.45 ± 0.68	0.51 ± 0.83	13.70 ± 0.75	1.31 ± 0.78
IF3	24.51 ± 0.92	0.39 ± 0.75	0.47 ± 0.72	17.02 ± 0.91	1.20 ± 0.84

*= values are expressed as mean ± SD, n=3

TABLE 5: MICROMETRIC PROPERTIES OF PURE DRUG AND SUSTAINED RELEASE CPT FORMULATIONS

Formulation Code	Angle of Repose (θ)*	Bulk Density (g/cm^3) *	Tapped Density (g/cc^3)*	Compressibility Index (%) *	Hausner's ratio*
Pure drug-CPT	29.36 ± 0.25	0.36 ± 0.46	0.42 ± 0.42	26.19 ± 0.54	1.35 ± 0.38
SR1	20.140 ± 0.31	0.28 ± 0.42	0.37 ± 0.56	24.32 ± 0.64	1.32 ± 0.42
SR2	21.32 ± 0.18	0.27 ± 0.63	0.35 ± 0.38	22.85 ± 0.73	1. 29 ± 0.52
SR3	21.17 ± 0.21	0.24 ± 0.87	0.30 ± 0.76	20.13 ± 0.63	1.25 ± 0.98
SR4	21.08 ± 0.98	0.26 ± 0.79	0.31 ±0.89	16.12 ± 0.29	1.19 ± 0.76
SR5	22.15 ± 1.20	0.29 ± 0.98	0.35 ± 0.54	17.14 ± 0.56	1.20 ± 0.59
SR6	23.11 ± 0.87	0.23 ± 0.45	0.29 ± 0.36	20.68 ± 0.78	1.26 ± 0.89
SR7	21.08 ± 0.31	0.28 ± 0.67	0.35 ± 0.72	23.20 ± 0.56	1.25 ± 0.72
SR8	21.47 ± 0.24	0.25 ± 0.54	0.31 ± 0.76	19.35 ± 0.76	1.24 ± 0.82

*= values are expressed as mean ± SD, n=3

Characterization of Solid Dispersions Parameters:

Determination of Drug Content and Percentage Yield: All the solid dispersions were in the form of free-flowing powders. The values of % drug content and % yield values were given in the **Table 6.** The % yield values of SD14 showed 99.6%, which is the highest among all the other formulations.

***In-vitro* Dissolution Studies:** The dissolution studies revealed that there was a notable difference between dissolution profile of pure drug ATR and ATR with carriers, as shown in **Table 7** and **Table 8.**

TABLE 6: DRUG CONTENT AND YIELD OF SDS

Formulation Code	Drug: Carrier	Drug Content (%)	% Yield
SD1	HP-β- Cyclodextrin (Physical mixture)	90.56±1.34	99.60±0.76
SD2		92.50±0.89	96.13±0.81
SD3		97.30±1.85	95.77±1.09
SD4		99.80±2.13	90.60±0.92
SD5	HP-β- cyclodextrin (Kneading method)	79.12±1.53	88.16±1.53
SD6		87.84±0.98	87.06±2.01
SD7		95.92±2.03	83.30±1.24
SD8		98.30±1.56	83.50±0.78
SD9	PEG 8000 (Physical mixture)	88.16±1.34	98.60±0.65
SD10		87.06±0.97	90.24±0.82
SD11		83.30±2.75	96.82±0.95
SD12		83.50±1.09	90.20±1.32
SD13	PEG 8000 (Kneading method)	99.60±1.53	95.33±0.19
SD14		96.13±2.34	94.08±3.10
SD15		95.77±1.87	94.05±2.56
SD16		90.60±0.84	95.00±2.98

Values are expressed as mean ± SD, n=3

TABLE 7: *IN-VITRO* DISSOLUTION OF ATR-SD'S BY USING HP-B-CYCLODEXTRIN

Time (min)	Cumulative % Drug Release	Physical Mixture (% Cumulative Drug Release)				Kneading Method (% Cumulative Drug Release)			
	Pure Drug	SD1	SD2	SD3	SD4	SD5	SD6	SD7	SD8
5	-	28.45 ±0.02	43.12 ±0.18	47.97 ±0.19	9.90 ±0.14	25.26 ±0.11	40.43 ±0.67	7.60 ±0.33	34.23 ±0.52
10	0.43 ±0.89	44.31 ±0.21	56.64 ±0.46	48.22 ±0.52	49.50 ±0.98	32.51 ±0.78	42.95 ±0.24	52.5 ±0.84	46.08 ±0.28
15	1.74 ±1.23	60.48 ±0.04	68.05 ±0.12	66.53 ±0.35	68.05 ±0.61	67.65 ±0.26	70.72 ±0.11	70.80 ±0.68	65.04 ±0.51
30	7.08 ±1.89	64.76 ±0.11	70.52 ±0.47	73.73 ±0.25	68.98 ±0.91	71.96 ±0.59	71.47 ±0.17	78.60 ±0.23	72.12 ±0.59
45	11.11 ±2.31	65.35 ±0.87	72.80 ±0.92	76.96 ±0.18	74.07 ±0.51	72.46 ±0.67	74.91 ±0.23	82.67 ±0.32	72.15 ±0.35
60	16.02 ±0.23	67.06 ±0.28	82.01 ±0.34	84.07 ±0.47	76.74 ±0.21	80.16 ±0.24	90.15 ±0.17	96.67 ±0.68	81.83 ±0.18

Values are expressed as mean ± SD, n=3

TABLE 8: *IN-VITRO* DISSOLUTION OF ATR-SD'S BY USING PEG 8000

Time* (min)	Physical Mixture (% Cumulative Drug Release			Kneading Method (% Cumulative Drug Release)				
	SD9	SD10	SD11	SD12	SD13	SD14	SD15	SD16
5	33.13±1.97	17.62±0.45	9.25±0.39	9.92±0.42	28.27±0.23	21.02±0.41	8.51±0.57	0.58±0.56
10	50.35±1.52	18.85±0.62	11.21±0.29	11.75±0.71	53.93±0.18	26.73±0.93	20.12±0.77	2.48±0.94
15	50.98±1.08	21.79±0.29	22.22±0.45	18.43±0.62	60.29±0.72	55.21±0.43	29.25±0.91	6.75±0.13
30	58.06±0.56	38.92±0.93	29.87±0.26	29.95±0.48	75.29±0.38	63.44±0.25	50.96±0.85	12.70±0.75
45	61.63±0.53	40.45±0.56	36.45±0.46	30.40±0.92	92.75±0.17	64.38±0.18	52.33±0.37	14.36±0.26
60	63.13±0.77	43.79±0.77	38.32±0.27	35.34±0.28	97.42±0.18	64.44±0.95	56.14±0.88	15.67±0.39

Values are expressed as mean ± SD, n=3

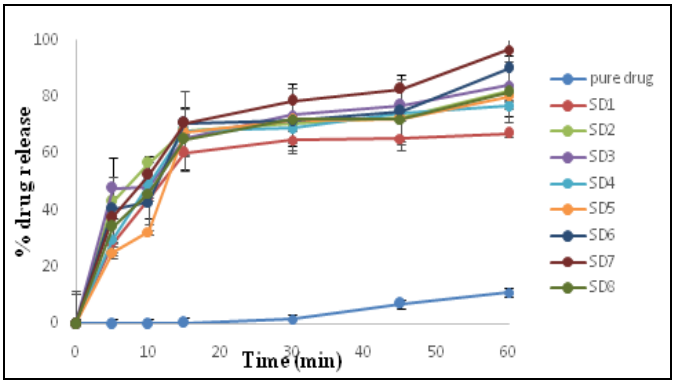

FIG. 19: *IN-VITRO* DISSOLUTION STUDIES OF PURE DRUG ATR AND SOLID DISPERSIONS (SD1-SD8)

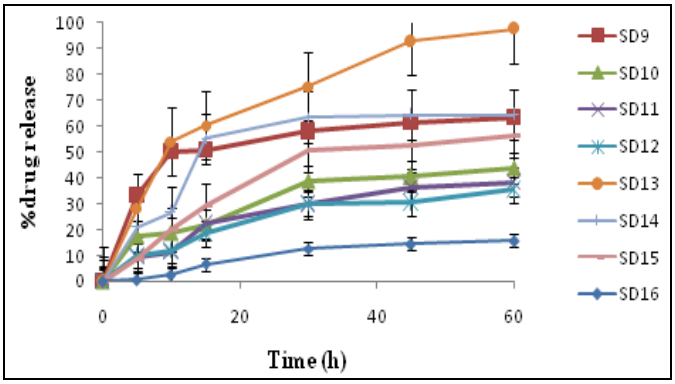

FIG. 20: *IN-VITRO* DISSOLUTION STUDIES OF PURE DRUG ATR AND SOLID DISPERSIONS (SD9-SD16)

Solid dispersion of ATR with PEG8000 carriers in the ratio of 1:0.25 (SD13) shown the highest % of drug release when compared to HP-β-Cyclodextrins. Hence it may be concluded that the ATR solubility is enhanced by the solid dispersion technique using the kneading method.

Post Compression Parameters: The hardness of prepared immediate and sustained-release tablets was in the range of (3.32 ± 0.17 to 6.26 ± 0.15 kg/cm^2) which indicated good mechanical strength.

The weight variation of prepared immediate release ATR layer in the range of 98.3 mg to 104.6 mg and floating sustained release layer was in the range of 289 mg to 327 mg in which none of the formulae was exceeding the limits of (± 5%) specified by USP.

The content uniformity of the prepared tablets was in the range of 96.4 ± 4.3 to 99.8 ± 1.76 %), which reveals a good content uniformity.

No tablets lie out of the range of 95%-115% of the label claim shown in **Table 9** and **Table 10**.

Determination of Floating Lag Time and Total Floating Time: The results of floating lag time (FLT) and total floating time (TFT) for all the prepared sustained-release formulations of floating tablets formulae are shown in **Table 10**. The immediate-release layer started dispersing in an initial 2 min; the tablet started tilting in 4 min, started floating at 5 min, the tablet was completely floated in 8 min and releasing the immediate release layer, the tablet remained floated for more than 12 h.

The formulation IF2 with crospovidone as super disintegrant had shown higher drug release of 96.98 % when compared to 76.53 % and 79.4 % noticed with IF1 and IF3 formulations with super disintegrants sodium starch glycolate and croscarmellose sodium respectively. Hence, formulation IF2 had been optimized.

TABLE 9: POST COMPRESSION PARAMETERS OF IMMEDIATE RELEASE TABLETS

Formulation Code	Average Weight (mg)* [a]	Hardness (Kg/cm^2)*[b]	Friability (%)* [c]	Drug Content (%)* [d]
IF1	104.6±1.34	3.6±0.72	0.62±0.37	98.23±0.79
IF2	102.9±0.98	3.8±0.89	0.54±0.65	102.30±0.95
IF3	98.3±1.21	4.2±0.83	0.58±0.75	99.56±0.83

(* =Values are expressed as mean ± SD, n=3), a= 20 tab, b=5 tab, c=10 tab, d=10 tab

TABLE 10: POST COMPRESSION PARAMETERS OF SUSTAINED RELEASE FLOATING TABLETS

Formulation Code	Average Weight (mg)[a*]	Hardness (kg/cm^2)[b*]	Friability (%[c*]	Drug Content (%)[d*]	Floating Lag time (s)[e*]	Total Floating time (h)
SR1	320±0.31	5.63±0.76	0.81±0.63	95.3±0.63	50±0.25	12
SR2	322±0.68	5.93±0.45	0.51±0.38	99.4±0.59	45±0.62	12
SR3	298±0.73	5.70±0.53	0.67±0.62	97.2±0.81	43±0.75	12
SR4	326±0.58	6.12±0.29	0.58±0.71	98.3±0.73	38±0.19	12
SR5	289±0.26	5.90±0.37	0.65±0.41	94.6±0.61	49±0.93	12
SR6	327±0.53	6.31±0.89	0.52±0.62	101.2±0.53	41±0.46	12
SR7	325±0.29	5.46±0.24	0.71±0.89	96.3±0.37	38±0.39	12
SR8	321±0.45	6.20±0.51	0.48±0.53	99.2±0.76	30±0.47	12

(* =Values are expressed as mean ± SD), n=3, a*= 20 tab, b*=5 tab, c*=10 tab, d*=10tab, e*=3 tab.

TABLE 11: *IN-VITRO* DISSOLUTION STUDIES OF IMMEDIATE RELEASE LAYER TABLET

Time (min)	% Cumulative Drug Release		
	IF1*	IF2*	IF3*
5	15.70±0.29	38.38±0.58	39.25±0.76
10	41.74±0.45	61.04±0.89	54.37±0.54
15	40.77±0.69	75.78±0.67	60.42±0.76
30	68.21±0.54	82.45±0.46	67.74±0.89
45	69.98±0.76	93.47±0.85	73.36±0.54
60	76.53±0.89	96.98±0.92	79.40±0.76

(* =Values are expressed as mean ± SD, n=3)

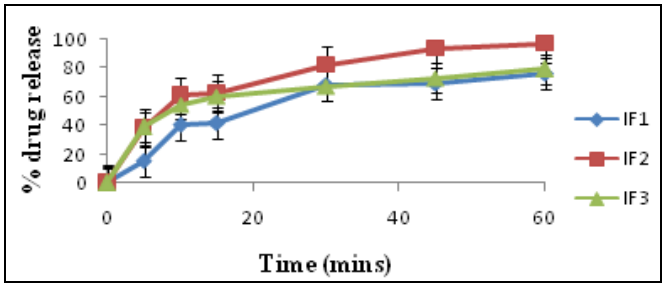

FIG. 21: *IN-VITRO* DISSOLUTION STUDIES OF IMMEDIATE RELEASE LAYER

TABLE 12: *IN-VITRO* DISSOLUTION STUDIES OF SUSTAINED RELEASE FORMULATION

Time (h)	% Cumulative Drug Release*							
	SR1	SR2	SR3	SR4	SR5	SR6	SR7	SR8
1	22.40±.032	18.68±1.87	0	0	23.40±0.43	21.40±0.62	19.92±0.49	20.53±1.38
2	30.56±0.24	22.97±1.52	20.24±0.34	17.44±0.91	28.90±0.53	29.34±0.51	29.56±0.32	28.42±0.85
3	35.42±0.35	39.03±1.84	27.62±0.65	28.91±0.47	34.01±0.49	36.34±0.59	37.05±0.53	35.5±0.50
4	46.85±0.27	44.20±0.9	34.58±0.44	36.58±0.54	39.80±1.53	46.12±0.44	44.02±0.35	44.89±0.62
5	49.85±0.54	62.28±1.62	45.61±0.32	40.23±0.55	44.08±2.03	52.54±0.39	50.18±0.48	52.68±0.56
6	56.38±1.45	64.21±0.91	53.05±0.46	45.74±0.37	49.80±1.7	59.25±0.25	57.74±0.83	66.67±2.30
7	60.24±0.62	71.10±0.89	58.03±0.39	53.82±0.49	52.98±1.52	63.75±0.28	60.85±0.95	70.66±1.39
8	65.54±0.74	77.20±1.89	60.41±0.20	59.91±0.39	61.27±0.97	69.13±0.16	69.97±0.96	74.24±1.24
9	72.31±1.25	84.16±1.53	62.42±0.43	65.04±0.20	67.97±2.56	73.52±0.59	72.71±0.65	76.28±2.76
10	75.31±2.54	90.14±1.36	66.03±0.42	71.38±0.43	72.04±1.51	78.56±0.76	75.86±0.51	79.83±0.9
11	78.91±1.47	94.28±0.87	74.02±0.23	78.51±0.42	79.37±1.85	85.69±0.32	81.43±0.37	81.59±2.31
12	85.63±2.32	98.20±0.78	79.68±0.63	82.98±0.23	86.30±2.17	92.72±0.92	90.02±2.10	96.76±2.31

*=Values are expressed as mean ± SD, n=3

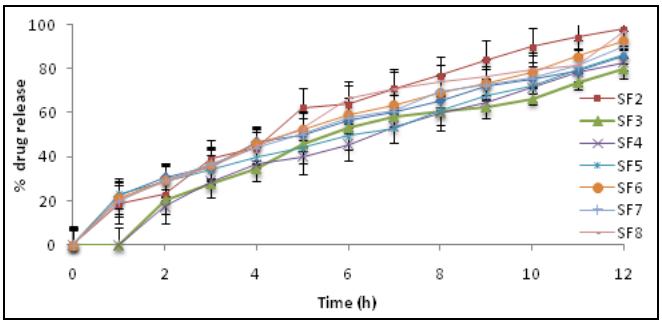

FIG. 22: *IN-VITRO* DISSOLUTION STUDIES OF SUSTAINED RELEASE FLOATING LAYER

***In-vitro* Dissolution Studies of Bilayer Floating Tablet:** Based on the drug release, the formulation IF2 and SF2 shown higher drug release than other formulations; hence these are optimized.

The other formulations containing carnauba wax SR1, SR3, SR4 released 85.63%, 79.68%, and 82.98% respectively, whereas formulation SR2 released a maximum of 98.2% in 60 min. The formulations SR5 to SR8 with cetyl alcohol released 86.3%, 92.72%, 90.02% and 96.76% respectively.

The Release Kinetics of optimized formulation (SF2) was fitted to models representing Zero order, First order, Korsmeyer-Peppas, Hixon-crowel. First-order release kinetics identified as the drug release mechanism. The data were treated for regression analysis by MS-EXCEL statistical function, as shown in **Fig. 23** to **Fig. 28.**

The results of the study show the *in vitro* release of the drug could be best expressed by first-order equation as the optimized formulation showed good linearity (r=0.987) values shown in **Table 13,** and that indicates the diffusion is a dominant mechanism of drug release with this formula.

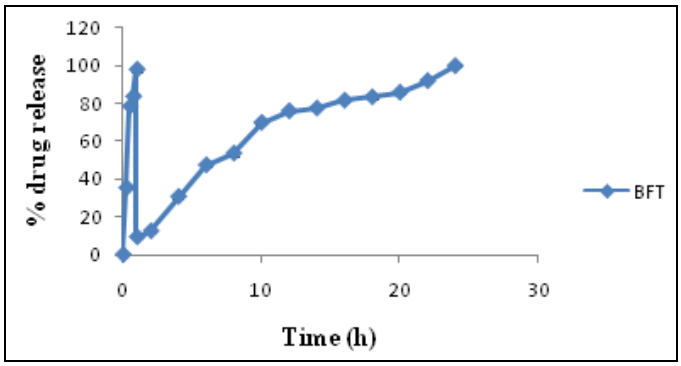

FIG. 23: *IN-VITRO* DISSOLUTION STUDIES OF BILAYER FLOATING TABLET

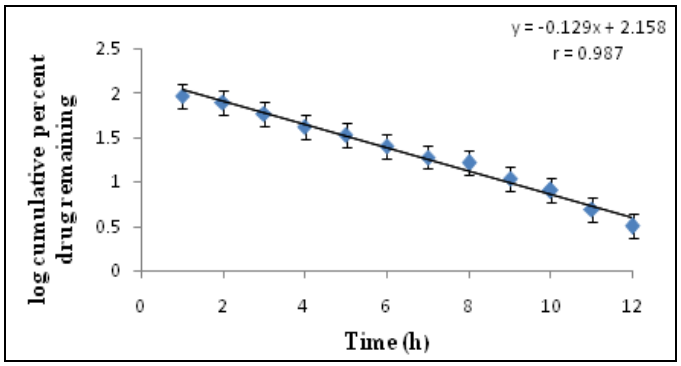

FIG. 24: FIRST ORDER PLOT OF OPTIMIZED SR2

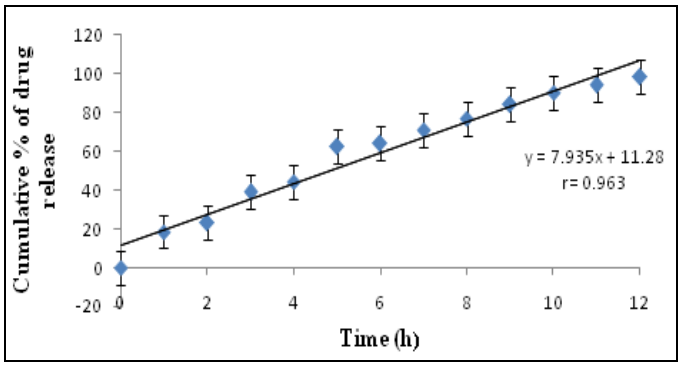

FIG. 25: ZERO ORDER PLOT OF SR2

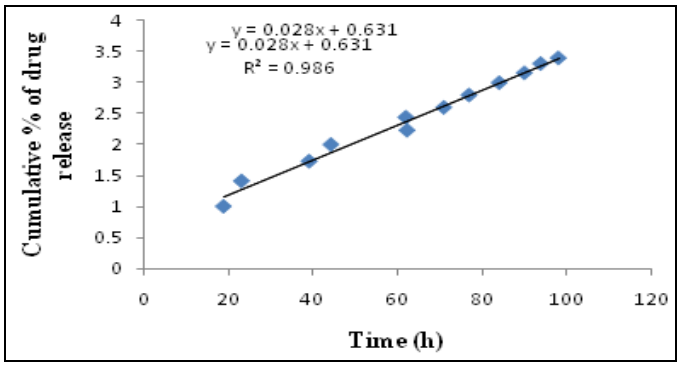

FIG. 26: HIGUCHI PLOT OF SR2

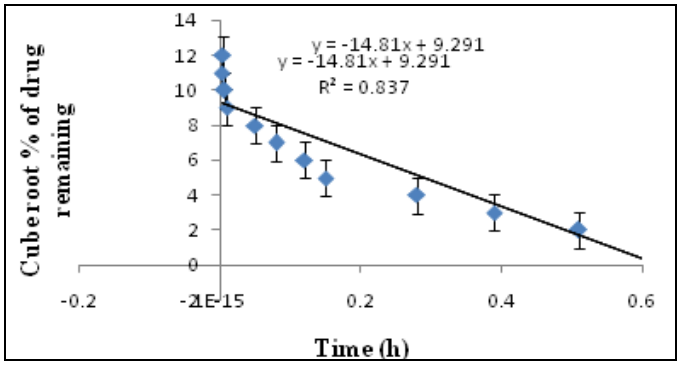

FIG. 27: HIXON CROWELL PLOT OF SR2

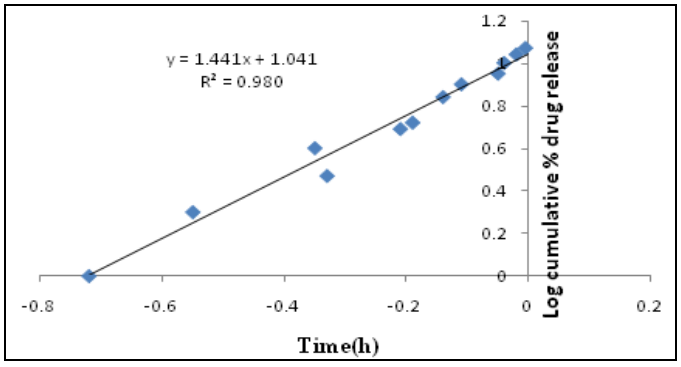

FIG. 28: KOSMEYER-PEPPAS PLOT OF SR2

TABLE 13: RELEASE KINETICS OF OPTIMIZED SR2 FORMULATION

Formulation Code (SR2)	r value
Zero-order	0.963
First-order	0.987
Higuchi model	0.986
Korsmeyer-peppas	0.980
Hixon Crowell plot	0.837

CONCLUSION: The formulation of bilayer floating tablet of sustained-release (12 h) floating layer of CPT (SR2) 25 mg was successfully achieved, which can be taken once daily thereby minimizing the side effect of steep fall in blood pressure and control its limitations which produce longer half-life and reduced dose frequency and possibly higher bioavailability. The immediate-release formulation of ATR (IF2) 10 mg gives immediate effect by releasing the drug within 1 h. Hence, the novel application of the floating technique can be applied for achieving sustained drug release.

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