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Formulation of Verapamil Hydrochloride Pellets by Extrusion-Spheronization Technology

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ABSTRACT : The objective of this study was to prepare and evaluate sustained release pellets of Verapamil Hydrochloride by using Extrusion - Spheronization method. The different formulations were prepared using HPMC, Dicalcium phosphate as synthetic polymers and MCC as spheronizing aid. Verapamil Hydrochloride is a phenylalkylamine calcium channel blocker which is used to treat high blood pressure. Lowering high blood pressure helps prevent strokes, heart attacks, and kidney problems. It works by relaxing blood vessels so blood can flow more easily. Verapamil is also used in angina pectoris. The formulated pellets were evaluated for various parameters like flow properties like Angle of repose, Bulk density and Tapped density, Carr's index, Hausner's ratio, drug content, in vitro drug release study. FTIR study confirmed the drug - polymer compatibility. The in vitro drug release of Verapamil Hydrochloride pellets was compared with that of marketed formulation. The three formulations were prepared using synthetic polymers HPMC, Dicalcium phosphate. The formulation F1 shows sustained release at end of 8 hrs was found to be 93.37±0.37%. The drug content was found to be in the range of 80.98±0.08% to 93.37±0.03%. It can be concluded that the developed formulation can be effective formulation with improved efficacy, promised release and patient compliance. Finally, we conclude that the developed formulation is effective with improved efficacy, promised release and patient compliance.

Key Words: Pellets, Verapamil Hydrochloride, Extrusion - Spheronization, HPMC.

I. INTRODUCTION:

The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body to achieve and maintain the desired drug concentration.[1] Several approaches existed for administration of drugs to the patients. In all those approaches oral administration has been received more attention due to more flexibility in designing of dosage forms.[2] Oral drug delivery is the most widely utilized route of administration among all the routes that have been explored for the systemic delivery of drug via pharmaceutical products of different dosage form. Oral route is considered most natural, uncomplicated, convenient and safe due to ease of administration, patient acceptance, and cost-effective manufacturing process.[3] Multi - particulate dosage forms (MPDFs) are receiving an immense attention as alternative drug delivery systems for oral drug delivery even though single unit dosage forms have been widely used for decades. The most commonly used pharmaceutical solid dosage forms today include granules, pellets, tablets and capsules.[4]

Hypertension sometimes called arterial hypertension is a chronic medical condition in which the blood pressure in the arteries is elevated. This requires the heart to work harder than normal to circulate blood through the blood vessels. Normal blood pressure at rest is within the range of 100-140 mm Hg for systolic and 60-90mm Hg for diastolic. High blood pressure is said to be present if it is persistently at or above 140/90 mmHg. Hypertension is a major risk factor for stroke, myocardial infarction (heart attacks), heart failure, aneurysms of the arteries, peripheral arterial disease and is a cause of chronic kidney disease.[5] Verapamil hydrochloride, a phenylalkylamine calcium-channel blocker, has broadly been used as an anti-arrhythmic drug to manage supraventricular tachyarrhythmias. Due its vasodilating and negative inotropic properties, it has been indicated for the treatment of hypertension, ischemic heart disease, and hypertrophic cardiomyopathy.[6]

Sustained release drug delivery

Sustained release technologies can improve the therapeutic efficacy and safety of a drug by precise temporal and spatial placement in the body, thereby reducing both the size and

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number of doses required. Furthermore, the possibility of repeating successful drugs, coupled with the increasing expense in bringing new drug entities to market, has been instrumental in generating interest in sustained-release dosage forms. The sustained release dosage form is defined as "any drug or dosage form modification that prolongs the therapeutic activity of the drug". Once the maximum level is reached, the amount of drug in the body decreases slowly so it will take longer to drop below the therapeutic range.[7]

Pellets

In the pharmaceutical industry, pellets can be defined as small, free-flowing, spherical particulates manufactured by the agglomeration of fine powders or granules of drug substances and excipients using appropriate processing equipment.[8] Pellets are spherical, free-flowing granules with a narrow size distribution, typically varying between 500 and 1500µm in size for pharmaceutical applications.[7]

Advantages of pellets

- Uniformity of dose.
- Controlled release application of pellets due to the ideal low surface area-to-volume ratio.
- Reduce inter and intra-patient variability.
- Modified-release multi particulate delivery systems are less susceptible to dose dumping than single unit dosage forms.

Disadvantages of pellets

- Requires highly sophisticated and specialized equipment.
- The control of manufacturing process is complicated with too many process variables as well as formulation variables.

Pelletization techniques[9]

The most commonly used and intensely investigated pelletization processes are powder Layering, solution/suspension layering, and extrusion-spheronization. Other pelletization processes that either have limited application include spherical agglomeration or balling, spray congealing drying, and emerging technologies such as cryopelletization and melt spheronization. The most commonly use pelletization processes are Extrusion spheronization, Hot melt extrusion, Solution or suspension layering, Powder layering, High shear pelletization, Freeze pelletization, Cryopelletization, Crystallo-co-agglomeration, Wet spherical agglomeration, Spherical crystallization etc.

Extrusion-Spheronization:

The extrusion-spheronization process is commonly used in the pharmaceutical industry to make uniformly sized spheroids. The main objective of the extrusion spheronization is to produce pellets/spheroids of uniform size with high drug loading capacity. Extrusion-spheronization is a multistep process involving dry mixing, wet granulation, extrusion, spheronization, drying, und screening.

Stages of Extrusion-Spheronization[10-12]

a) Dry mixing

Dry mixing of all ingredients is done to get homogeneous powder dispersion or mixer using different types of mixers like twin shell blender, high shear mixer, tumbler mixer and planetary mixer.

b) Wet massing

This process of powder dispersion is done to produce a sufficient plastic mass for Extrusion. It is similar to the wet granulation method. The most commonly used granulator is planetary mixer or sigma blade mixer or high shear mixer and Horbat mixer.

c) Extrusion

It is the method of applying the pressure to wet mass to pass/flow through the openings of the extruder to get rod shaped particles and bonding of wet mass obtained by solvent system. Extrudate should have enough plasticity to deform but not to adhere in spheronization operation. The granulation solvent serves as the binding agent to form the granules and as the lubricating during the extrusion operation.

d) Spheronization

The instrument used is called Spheronizer where the extrudate is rotated at higher speed by friction plate that breaks the rod shaped particles in to smaller particles and rounded them to form spheres. The spheronization operation has been divided into 3 stages:-

- Breaking of cylindrical segments or extrudates
- Agglomeration of broken segments
- Smoothing of particles

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e) Drying

The ideal pellets are obtained by roper drying either at room temperature or elevated temperature in a tray dryer or in a fluidized bed dryer. The freeze drying method retains the shape and size and the granules whereas the oven drying produce rough granules.

f) Screening

It is necessary to achieve the desired size distribution and for this purpose sieves are used. Based on the type of feed mechanism and to transfer the mass towards the die, Variety of extruders is used. Thus, the aim of present study is to prepare and evaluate sustained release pellets of Verapamil Hydrochloride by using Extrusion - Spheronization technique.

II. METHODOLOGY

Materials and equipment's:

List of Materials used: Verapamil Hydrochloride HPMC K4M MCC Dibasic Calcium Phosphate Yarrow chem products, Mumbai**.**

Methods:[13-17]

Pre-formulation studies:

Organoleptic evaluation, Colour and nature, Melting point were determined as per the standard procedure.

Determination of absorption maxima of Verapamil Hydrochloride in 0.1 N HCl: Standard stock solution, 30 µg/ml solution was scanned by using UV spectrophotometer in the range of 200-400 nm.

Calibration curve of Verapamil Hydrochloride in 0.1 N HCl: Measured the absorbance of the 5,10, 15, 20 and 25 µg/ml prepared standard solution at λ_{max}. Graph was plotted concentration (µg/ml) on X axis and absorbance on Y axis. Slope and Regression coefficient values were calculated.

Compatibility Study:

FTIR spectroscopy was carried out to check the compatibility between drug and the excipeinets. The FTIR spectra of drug with polymers were compared with the standard FTIR spectrum of the pure drug. The scanning range was 4000–400 cm^{-1}. The spectra obtained were compared and interpreted for the functional group peaks.

Formulation of pellets: [18-20]

Mix the weighed quantity of drug and excipients to get homogeneous powder dispersion. Wet massing was done to produce a sufficient plastic mass. Place the wet mass in the extruder, where it continuously forms into a cylindrical rod of uniform shape. After the extrudate is partially dried and spheronized at speed of 800-900 rpm in a spheronizer. The friction plate breaks the rod-shape particles into smaller particles and rounded them as spheres. The pellets were dried in trays at room temperature.

Table 1: Formulation chart for preparation of Verapamil Hydrochloride pellets

Sl. No.	Ingredients	Formulations (g)		
		F1	F2	F3
1	Verapamil Hydrochloride	1.00	1.00	1.00
2	HPMC K4M	0.5	0.25	0.75
3	MCC	4.5	4.75	4.25
4	Dibasic Calcium Phosphate	4	4	4
5	Water	q.s	q.s	q.s

Evaluation of prepared pellets of Verapamil Hydrochloride:[21-26]

Derived Properties: All formulations were evaluated for Flow properties like Angle of repose, Bulk density, Tapped density, Hausner's ratio and Carr's index and reported.

Drug Content: The pellets (500mg) were weighed and crushed in a mortar and pestle. Out of this, weigh 150 mg and transfer it into a 100 ml volumetric flask. Add little amount of 0.1 N HCl. Sonicate this solution for 5 minutes. Then make up the volume to 100 ml using 0.1 N HCl. Filter using Whatman filter paper. Then take about 1.5 ml of filtrate into 10 ml volumetric flask and raise using 0.1 N HCl. Verapamil Hydrochloride content was estimated by UV spectrophotometer at 228.4 nm. The drug content was determined.

In- vitro dissolution studies using phosphate buffer 6.8 pH:[27-31] Freshly prepared 900 ml of Phosphate buffer pH 6.8 was placed in dissolution

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vessels of dissolution test apparatus USP II (Paddle) model. The medium was allowed to equilibrate to 37.0±0.5ºC. 0.17 g of pellets were placed in the vessel, then the apparatus was operated for 8 hours at 50 rpm. At definite intervals, 5 ml of the receptor fluid was withdrawn, filtered and again 5 ml receptor fluid was replaced and analysed spectrophotometrically at 228.4 nm using UV- spectrophotometer.

Dissolution parameters:

- Media –900 ml pH 6.8 phosphate buffer
- Apparatus – USP Type II (Paddle)
- RPM – 50 rpm
- Amount of media - 900 ml
- Temperature – 37.0 ±0.5 ºC

III. RESULTS:

Pre-formulation study of Verapamil Hydrochloride:

Table 2: Organoleptic characteristics, Solubility and melting point of Verapamil Hydrochloride

Properties	Reported	Result
Description	Solid,White, crystalline powder	Solid, White, crystalline powder
Odor	Odourless	Odourless
Melting Point	140° - 144°	141°
Solubility	Freely soluble in chloroform; soluble in water, sparingly soluble in ethanol (95 per cent); practically insoluble in ether.	Complies

Determination of λ_{max}:

This is performed by using UV spectrophotometer by using Phosphate buffer pH 6.8 as medium. Maximum absorbance was found at 228.4 nm as shown in the UV spectra.

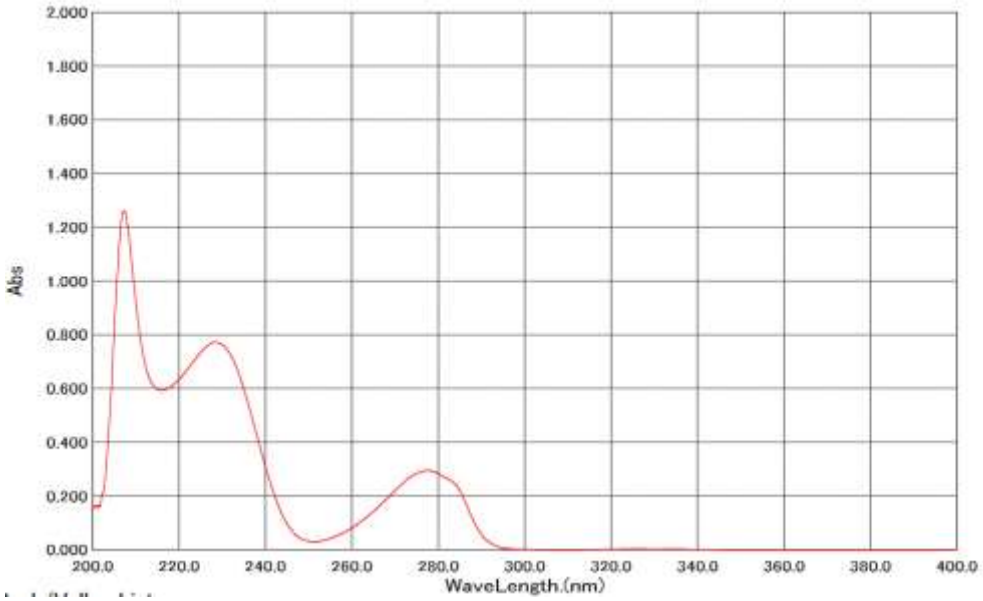

Fig 1: Determination of λmax

Standard Calibration Curve using 0.1N HCl as Solvent:

Standard calibration curve was constructed in the concentration range of 0-25µg/ml.

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Table 3: Standard graph of Verapamil Hydrochloride

Sl. No.	Concentration (µg/ml)	Absorbance*
1	0	0.000±0.00
2	05	0.278±0.003
3	10	0.446±0.008
4	15	0.624±0.005
5	20	0.845±0.016
6	25	0.975±0.011

*All the values are expressed as mean; n=3

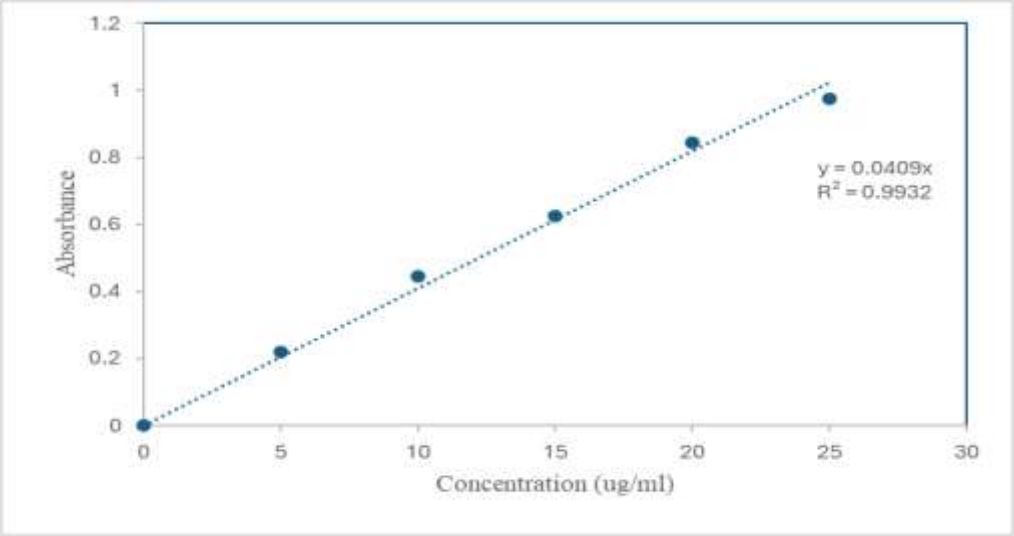

Fig 2: Standard Calibration Curve for Verapamil Hydrochloride

Evaluation Parameters for pellets:

1. Derived Properties: All formulations were subjected to Flow properties like Angle of repose, Bulk density, Tapped density, Hausner's ratio and Carr's index and results are discussed below.

Table 4: Evaluation of flow properties of pellets

Batch No.	Angle of Repose* (θ)	Bulk density* (gm/cc)	Tapped density* (gm/cc)	Hausner's ratio*	Carr's index* (%)
F1	$24^0$49'±0.12	0.8474±0.005	0.9259±0.008	1.09±0.032	8.47±0.002
F2	$23^0$88'±0.14	0.8620±0.006	0.9433±0.006	1.09±0.057	8.62±0.006
F3	$24^0$10'±0.12	0.8333±0.005	0.8928±0.007	1.07±0.013	6.66±0.005

*Data expressed as a mean ±SD, n=3

2. Drug content:

The drug loaded pellets of Verapamil Hydrochloride prepared. Drug content of all batches are as shown in Table.

Table 5: Drug content

Batch	Drug Content (%mean ±SD) *
F1	80.98±0.08
F2	93.37±0.03
F3	86.85±0.03

*All the values are expressed as mean; n=3

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3. Drug - Excipient Compatibility Study:-

Compatibility studies were performed using FTIR spectroscopy. The peaks obtained in the spectra of physical mixture were correlated with peaks of drug spectrum.

FTIR spectra of Verapamil Hydrochloride

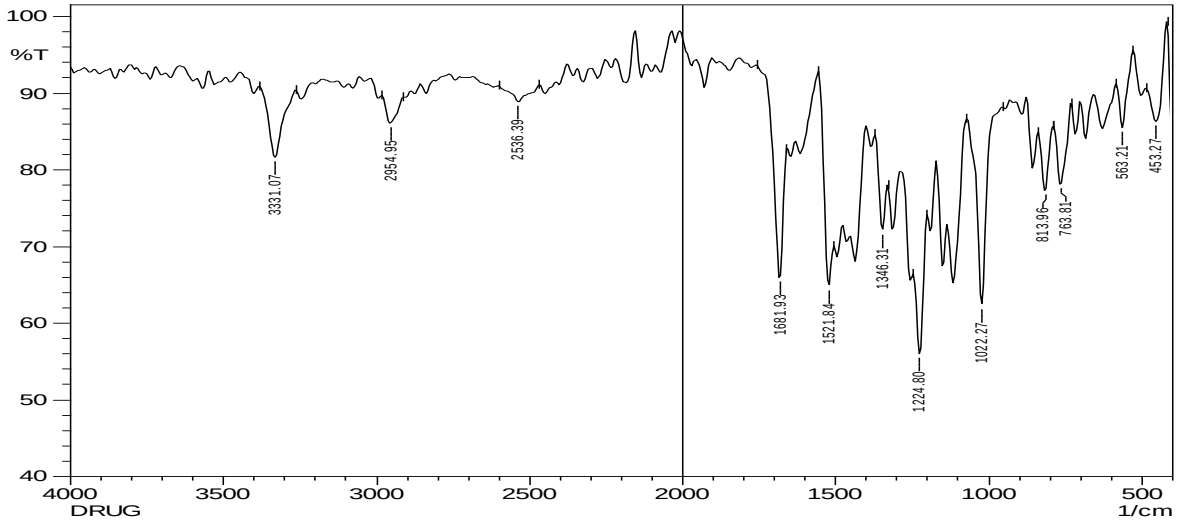

Fig 3: FTIR spectra of Verapamil Hydrochloride

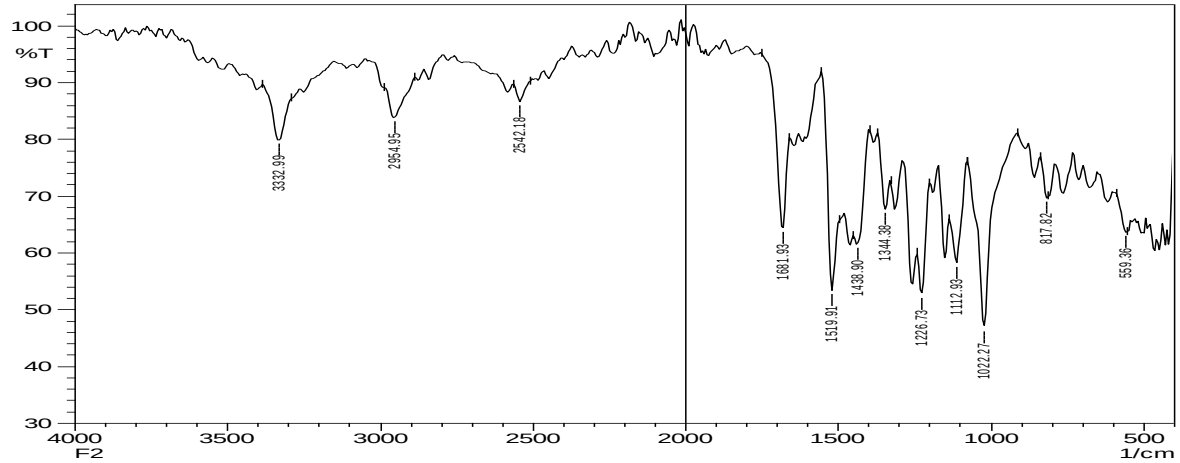

Fig 4: FTIR spectra of mixture containing Verapamil Hydrochloride, MCC, HPMC K4M and Dicalcium phosphate (F2)

Table No. 11: Interpretation of FTIR result

Sl. No.	Functional Group Stretching	Characteristic Wave Number (cm^{-1})	Observed Frequency(cm^{-1})	
			Pure Drug (cm^{-1})	Drug + HPMC K4M + DCP
1	N-H	3300-3500	3331.07	3332.99
2	C-H	2800-3000	2954.95	2954.95
3	C=C	1450-1600	1521.84	1519.41
4	C-N	1200-1350	1224.80	1226.73
5	C-O	1000-1300	1022.27	1022.27
6	C-Cl	600-800	763.81	764.91

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4. In-vitro dissolution study:

Table 6: In-vitro dissolution studies of formulations

Time (hours)	Percentage Cumulative Drug Release(%CDR) (%mean ± SD)		
	F1	**F2**	**F3**
0	0	0	0
0.5	14.32±0.16	16.91±0.20	12.33±0.29
1	19.59±0.21	23.95±0.44	17.00±0.36
2	26.30±0.39	32.97±0.29	22.84±0.44
3	35.26±0.61	48.03±0.19	29.02±0.59
4	42.56±0.78	52.03±0.10	36.78±0.64
5	48.76±0.64	60.83±0.95	42.59±0.98
6	54.91±0.79	66.76±0.18	51.05±0.71
7	62.00±0.59	74.70±0.82	59.50±0.87
8	71.52±0.67	80.59±0.21	67.54±0.33

*All the values are expressed as mean; n=3

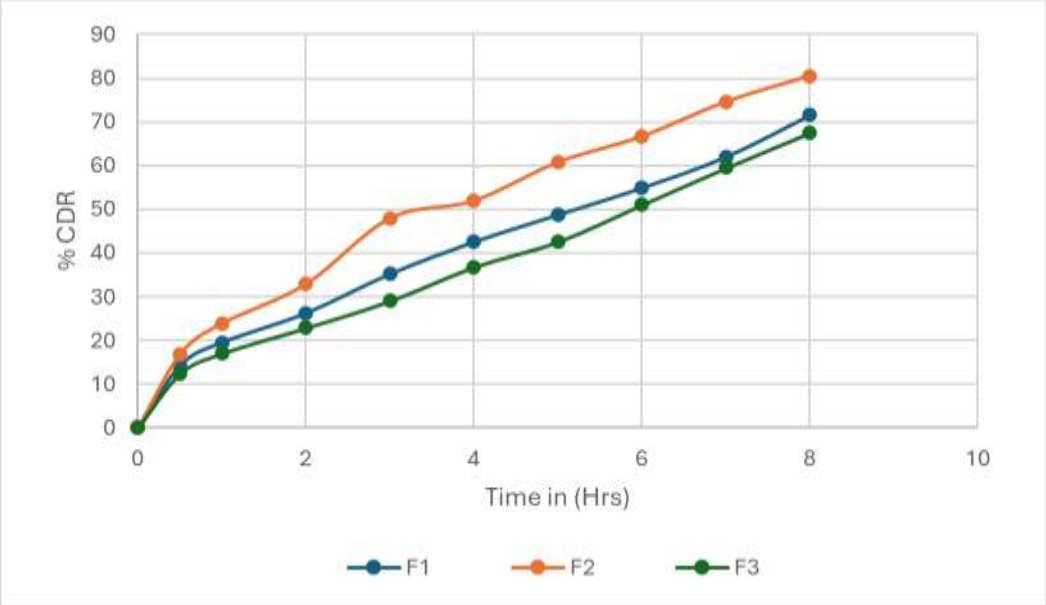

Fig 5: In-vitro dissolution studies of Verapamil Hydrochloride pellets

The present investigation focused on the formulation and evaluation of sustained release pellets of Verapamil Hydrochloride using Hydroxypropyl Methylcellulose (HPMC) and Dicalcium Phosphate as polymers. Pellets were successfully prepared by the extrusion–spheronization technique. Preformulation studies confirmed drug identity and compatibility with

polymers through FTIR, showing no interaction. Verapamil Hydrochloride showed a characteristic absorption maximum at 228.4 nm in 0.1 N HCl. Calibration curves in the concentration range of 0–25 µg/ml was linear, with correlation coefficients of 0.99 confirming adherence to Beer–Lambert's law. All the derived properties of powder found within the limit. Drug content analysis of formulations F1–F3 ranged from 80.98% to 93.37%. In-vitro dissolution studies demonstrated sustained drug release over 08 hours, with formulation F2 showing the highest drug release of 80.59±0.21% at the end of 08 hours. These results confirm that the prepared pellets can maintain therapeutic drug levels for an extended duration and thereby improve patient compliance. These results confirm that the prepared pellets can maintain therapeutic drug levels for an extended duration and thereby improve patient compliance.

IV. CONCLUSION

From this study, it can be concluded that Sustained release pellets of Verapamil Hydrochloride can be prepared using the extrusion–spheronization method. Preformulation and evaluation studies confirmed good flow properties, mechanical stability, and acceptable drug content in all formulations. Formulation F2 demonstrated the most promising sustained release profile with 93.37% drug release in 12 hours, meeting the desired therapeutic goals. Thus, the developed sustained release pellet formulation of Verapamil Hydrochloride offers a reliable dosage form with improved efficacy, prolonged drug release, reduced dosing frequency, and better patient compliance.

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