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FORMULATION, DEVELOPMENT AND EVALUATION OF SUBLINGUAL ANTI-EMETIC TABLET BY MELT GRANULATION TECHNIQUE

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Keywords:

Prochlorperazine maleate, Emesis, Sublingual, Melt granulation, Solubility, binders

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ABSTRACT: Prochlorperazine maleate is used for the treatment of motion sickness and classified under BCS class II for treatment of emesis, the per-oral route is preferred route of administration but first-pass effect and poor bioavailability limits its application. To overcome these limitations, efforts were made to enhance the bioavailability of drugs via the development of a sublingual tablet by melt granulation technique. The formulation was developed by the melt granulation method where PEG 6000 and PEG 400 blend and gelucire as a hydrophilic polymer were used to enhance solubility and drug release rate. The tablets were evaluated for hardness, thickness, friability, weight variation, drug content, wetting time, *in-vitro* disintegration time and water absorption ratio, and *in-vitro* dissolution studies. It was concluded that sublingual tablets containing sugar: PEG ratio drug, and lactose showed the highest drug release in the *in-vitro* dissolution studies. The optimized batch was subjected to accelerated stability studies. No change in physicochemical properties as well as in drug content and *in-vitro* release studies were observed.

INTRODUCTION: A fast-dissolving sublingual tablet system can be defined as a dosage form for oral administration, which, when placed in the mouth, rapidly dispersed or dissolved and can be swallowed in the form of liquid. Recently fast dissolving formulation is popular as NDDS because they are easy to administer and lead to better patient compliance. The pediatric and geriatric patient has difficulty in swallowing the conventional dosage forms. These dosage forms dissolve or disintegrate in the oral cavity within a minute without the need for water or chewing. For these formulations, the small volume of saliva is usually sufficient to result in tablet disintegration in the oral cavity [1].

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The medication can then be absorbed partially or entirely into the systemic circulation from blood vessels in the sublingual mucosa, or it can be swallowed as a solution to be absorbed from the gastrointestinal tract [2]. Orally administered dosage forms are challenging to formulate if the active substances have poor dissolution or low bioavailability. The enhancement of oral bioavailability of poorly water-soluble drugs remains one of the most challenging aspects of drug development. There are many methods to enhance drug solubility and bioavailability, in which one of the methods is melt granulation technique [3].

The melt granulation technique is a process by which pharmaceutical powders are efficiently agglomerated by the use of a low melting point binder, which is added to the other components of the powder. Once in a molten state, the binder acts as a granulating liquid. The temperature of the mixture is raised to above the melting point of the binder, either by a heating jacket, or by the heat of

friction generated by the impeller blades [3]. (Sustained-release dosage forms can be prepared by this process through using a lipophilic binder as glyceryl monostearate [4], stearic acid [5], or a combination of hydroxypropyl methylcellulose and hydrophobic polymers [6].

It also can be used to prepare fast-release formulations by using a water-soluble binder as polyethylene glycol (PEG) [7] and Gelucire. Anti-Emetic drugs which are widely used in the prevention and treatment of nausea, vomiting including that associated with migraine or drug-induced emesis is available as a conventional tablet, buccal tablet as solid dosage form, but tablet dosage form drug gives slow onset of action and less bioavailability. Therefore, to formulate drugs as a sublingual tablet by melt granulation technique may be a solution to address this problem.

Prochlorperazine (Compazine, stemzine, buccastem, stemetil, phenotil) is a dopamine (D2) receptor antagonist that belongs to the phenothiazine class of antipsychotic agents which is used for the antiemetic treatment of nausea and vertigo. It is also used to treat migraine headaches. For the quick absorption of the sublingual drug, the route is very well known.

Prochlorperazine maleate is a weakly basic BCS class II drug having poor aqueous solubility. When given orally, it undergoes the first-pass metabolism, which amounts to poor bioavailability.

Therefore, in the present research work, sublingual tablets of Prochlorperazine maleate by melt granulation technique will be prepared. In the melt granulation technique, various melt able hydrophilic binders are used, which helps in improving the wet ability of the drug leading to the fast disintegration of tablets and subsequently enhances dissolution of the drug. Melt granulation technique further reduces the processing steps and time in the manufacturing of tablets [8].

MATERIALS: Drug Sample Prochlorperazine Maleate and Excipients such Polyethylene glycol 400 and 6000, Granular Mannitol (Pearlitol), Silicified Microcrystalline Cellulose (Prosolv) and Natrosol (Hydroxyethyl Cellulose) as were a generous gift from Zim Laboratories and solvents used were of analytical grade.

METHODS:

Analytical Methods for Determination of PCPM: Developed formulations of Prochlor-perazine Maleate (PCPM) were analyzed using UV spectrophotometric method. The calibration curves were prepared in 6.8 saline phosphate buffer.

UV Spectrophotometric Analysis of PCPM:

Preparation of Stock Solution: About 50 mg of PCPM was weighed accurately and was then dissolved in 6.8 pH saline phosphate buffers in a 50 ml volumetric flask to prepare a stock solution having concentration 1000 µg/ml. From this 1 ml solution was pipetted out and diluted up to 10ml using 6.8 pH saline phosphate buffers to form a solution having a concentration of 100 µg/ml.

Preparation of Working Standard Solutions: About 0.5, 1, 1.5, 2, 2.5 and 3 ml aliquots were taken from the stock solution and diluted separately with 6.8 pH saline phosphate buffers in 10 ml volumetric flasks to prepare the series of working standard solutions in a concentration range of 5 to 30 µg/ml.

Analysis of Working Standards: The absorbance of working standard solutions of PCPM was taken at 258 nm. Calibration curves were constructed by plotting the absorbance against the concentration of drug in µg/ml. The linear relationship was evaluated by calculation f the regression line by the method of least squares. The R^2 values for PCPM calibration curves were found out to be 0.998 in 6.8 saline phosphate buffers.

Drug-Excipient Compatibility Studies: To use various excipients to develop the formulation, it is always necessary to carry out preformulation studies to check compatibility between drug and chosen excipients. Drug powder in its dry state was mixed using mortar and pestle with various excipients to obtain physical mixtures and stored in sealed glass vials at 40 ºC / 75% RH for two days and was subjected to IR and DSC studies.

Fourier Transform Infrared Spectroscopy (FTIR): Infrared spectroscopy was conducted using a Shimadzu FTIR 8300 spectrophotometer, and the spectrum was recorded in the region of 4000 to 400 cm^{-1}. Samples (drug alone and formulation) were mixed with potassium bromide (200-400 mg) and compressed into discs by

applying a pressure of 5 tons for 5 min in a hydraulic press. The compressed disc was placed in the light path, and the spectrum was obtained.

Differential Scanning Calorimetry (DSC): The physical state of PCPM in Granulation Form was characterized by Differential scanning calorimetry. The samples were placed in a standard aluminum pan, and dry nitrogen was used as effluent gas. All the samples were scanned at a temperature speed of 100 ºC/min and heat flow from 0 to 80 ºC. DSC was performed using NETZSCH DSC to study the thermal behavior of drug alone and prepared optimized formulation.

Formulation of Sublingual Tablets by Melt Granulation Technique:

Optimization of Blend of PEG 400 and PEG 6000 (Meltable binder): PEG has been widely used in melt granulation because of its favorable solution properties, low-melting-point, rapid solidification rate, low toxicity, and low cost. PEG 400 was mixed with PEG 6000 at ratios of 1:1, 2:8, 3:7, 4:6, 5:5 weight ratios. These blends were melted on a water bath until homogeneous, then removed from the bath and triturated until congealed. The melting points of the resulting mixtures were determined using the capillary method. Mixtures which produced a melting point around 37 °C and 35 °C were being used for granulation preparation [9].

Optimization of Sugar: PEG Ratios: Sugars have not only good compatibility but also have good solubility, which will help in faster disintegration of the tablet. In the present formulation, directly compressible Mannitol (Pearlitol SD 200) was used as a diluent as well as a sweetener to enhance mouth- feel. Sugar was mixed with two PEG blends, *i.e.,* Blend 1 with a melting point of 37 °C and Blend 2 with a melting point of 35 °C at the following weight ratios 1:1, 2:1, 3:1, 4:1, 5:1 respectively. PEG blends were heated at 40 °C in a water bath. Sugar was added to the molten mass and stirred at 100 rpm for 5 min using a High Shear Mixer. The mixture was continuously stirred until complete cooling.

Study of Compressibility of Prepared Meltable Granules: Granules obtained from the above procedure were mixed with other tablet additives geometrically. The amount of drug in each formulation was kept constant, *i.e.,* 5 mg PCPM per tablet, PEG as a meltable binder combination with sugar, Avicel pH 102 (Microcrystalline cellulose) as a diluent, Ac-di-sol (Croscarmellose sodium) as a super disintegrant and Orange flavor were used. The mixture followed by mixing for two minutes. The obtained blend was compressed into a tablet of 100 mg using 8 mm round flat punches on 12 stations rotary tablet machine.

TABLE 1: PCPM FORMULATIONS CONTAINING DIFFERENT SUGAR: PEG RATIOS

Formulation code	A	B	C	D	E
Sugar: PEG ratio →	1:1 (42.3%)	2:1(42.3%)	3:1(42.3%)	4:1(42.3%)	5:1 (42.3%)
Orange flavor	1.2%	1.2%	1.2%	1.2%	1.2%
Avicel pH 102	46.5%	46.5%	46.5%	46.5%	46.5%
Ac-di-sol	5%	5%	5%	5%	5%

Preparation of Granules by using Meltable Binders:

PEG Blend used as Meltable Binder: The optimized PEG blend: sugar ratio obtained from the above procedure. The granules were prepared in a laboratory-scale jacketed high shear mixer connected to a recirculating water bath to maintain a constant temperature. PCPM was mixed with either lactose or Avicel pH 102 (Microcrystalline Cellulose) with Ac-Di-Sol (Cross Carmellose Sodium) for 5 min at approximately 20,000 rpm. The temperature was then increased to 60 ºC and maintained at for the entire granulation. PEG blend: sugar ratio, was then added to the dry blend and mixed until a suitable granulation was obtained. At the end of the granulation process, the granules were allowed to cool at room temperature and then passed through a 30-mesh sieve. Granules contain 5% PCPM.

Gelucire used as a Meltable Binder: Using Gelucire as a meltable binder, six formulations were prepared. The formulation compositions are as shown in **Table 3**. The granules were prepared in a laboratory-scale jacketed high shear mixer connected to a recirculating water bath to maintain

constant temperature. PCPM was mixed with either lactose or Avicel pH 102 with Ac-Di-Sol for 5 min at approximately 20,000 rpm. The temperature was then increased to 60 ºC and maintained at for the entire granulation. The binder, Gelucire 44/14, was then added to the dry blend and mixed until a suitable granulation was obtained. At the end of the granulation process, the granules were allowed to cool at room temperature and then passed through a 30-mesh sieve. Granules contain 5% PCPM [10].

TABLE 2: GRANULES PREPARED BY PEG BLEND AS A MELTABLE BINDER

Formulation code →	PEG F1	PEG F2	PEG F3	PEG F4	PEG F5	PEGF6
Sugar: PEG ratio	3:1 (30%)	3:1(35%)	3:1(40%)	3:1(30%)	3:1(35%)	3:1(40%)
Orange flavour	1.2%	1.2%	1.2%	1.2%	1.2%	1.2%
Avicel pH 102	58.8%	53.8%	48.8%	-	-	-
Lactose	-	-	-	58.8%	53.8%	48.8%
Ac-di-sol	5%	5%	5%	5%	5%	5%

TABLE 3: GRANULES PREPARED BY GELUCIRE AS A MELTABLE BINDER

Formulation code →	GF1	GF2	GF3	GF4	GF5	GF6
Gelucire	30%	35%	40%	30%	35%	40%
Orange flavour	1.2%	1.2%	1.2%	1.2%	1.2%	1.2%
Avicel pH 102	58.8%	53.8%	48.8%	-	-	-
Lactose	-	-	-	58.8%	53.8%	48.8%
Ac-di-sol	5%	5%	5%	5%	5%	5%

Evaluation of Granules:

Effect of Meltable Binders on *In-vitro* Dissolution Profile of PCPM: The prepared granules of PEG blend & Gelucire were subjected to an *in-vitro* dissolution test. Weighed accurately a quantity of the Granules equivalent to about 5 mg of PCPM for dissolution testing. The dissolution test was performed in a USP XXI Dissolution Test Apparatus-II (Electrolab) paddle method in 900 ml Phosphate buffer pH 6.8 maintained at 37 ± .5 ºC, at 50 rpm. 5 ml sample was withdrawn at each predetermined time interval. The volume with-drawn at each interval was replaced with 5 ml of fresh dissolution medium. The collected samples were suitably diluted and absorbance was measured spectrophotometrically at 258 nm. The percentage of PCPM released at various time intervals was calculated and plotted against time. The results shown for dissolution studies are the average of three determinations.

Preparation of Tablets by using Gelucire (Hydrophilic Meltable Binder): Another commonly used binder is Gelucire®, which is a mixture of glycerides and fatty acid esters of PEGs. Gelucire® has shown to further increase the dissolution rate of poorly water-soluble drugs, attributed to the surface-active and self-emulsifying properties. In the above formula, PEG was replaced by another meltable binder *i.e.,* Gelucire. The amount of drug in each formulation was kept constant *i.e.*5 mg PCPM per tablet.

TABLE 4: PCPM FORMULATIONS CONTAINING GELUCIRE

Formulation code →	GPF1	GPF2	GPF3	GPF4	GPF5
Gelucire	25%	30%	35%	40%	45%
Orange flavour	1.2%	1.2%	1.2%	1.2%	1.2%
Avicel pH 102	63.8%	58.8%	53.8%	48.8%	43.8%
Ac-di-sol	5%	5%	5%	5%	5%

Effect of Various Excipients on Compression Properties of Granules: Once the granules were prepared using the melt granulation method, various excipients for improving flow properties, as well as various sugars, were used in the formula and their effects were observed on the compression properties of granules. From the literature survey, we found that Sucrose is hygroscopic, especially at elevated temperatures and high humidity. Mannitol, however, has low hygroscopicity and allows a short disintegration time, yet possesses low compressibility and results in a soft tablet. Granulation of mannitol improves its compressibility. Consequently, the tablets were formulated using granular mannitol alone or in combination with sucrose. A mixture of mannitol and sucrose has excellent flow and compression properties: produced tablets are hard, with smooth

surfaces and low friability. Also, inclusion of Prosolv® into formulation improves flow properties, yet causes an increase in the disintegration time. In the present investigation we also tried Natrosol (hydroxyethyl cellulose - a non-ionic, water -soluble polymer) in addition to prosolv. Formulations FP1-FP8 contains excipients as follows

TABLE 5: PCPM FORMULATIONS FP1 TO FP8 CONTAINING VARIOUS EXCIPIENTS (WEIGHT IN mg)

Formulation Code →	FP1	FP2	FP3	FP4	FP5	FP6	FP7	FP8
Sugar	*G.M	G.M	G.M	G.M	G.M	G.M	#S/G.M	S/G.M
Sugar: PEG blend	3:1	3:1	3:1	3:1	3:1	3:1	3:1	3:1
Drug	5	5	5	5	5	5	5	5
Avicel pH 102	20	5	10	25	20	33	38.3	33
Ac-di-sol	5	7	9	3	7	7	7	7
Natrosol	30	30	30	30	-	-	-	-
Prosolv	-	-	-	-	30	15	30	30
Orange flavour	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2
Magnesium stearate	1.5	1.5	1.5	1.5	0.5	0.5	0.5	0.5

*G. M: Granular mannitol, #S/G.M: Sucrose/ Granular mannitol (1:1 ratio)

Optimized Tablet Formulation: The above investigations were carried out to find out optimized concentrations, blends, and types of excipients for the final formulation of sublingual tablets by the melt granulation technique. Pre-compression parameters of the granules prepared using optimized formulation were studied. Tablets were compressed using those granules which passed all the evaluation parameters. These tablets were then evaluated for post-compression parameters. Tablets were compressed using 8mm round flat punches on 12 stations rotary tablet machine. **Table 6** shows the formulation table.

TABLE 6: PCPM FORMULATION FROM F1 TO F8 (WEIGHT IN mg)

Formulation code →	F1	F2	F3	F4	F5	F6	F7	F8
Sugar: PEG blend (Ratio)	3:0.25	3:1	3:0.25	3:0.25	3:1	3:1	3:0.25	3:1
PCPM	5	5	5	5	5	5	5	5
Sugar: PEG	38	38	38	38	38	38	38	38
Prosolv	10	10	30	10	30	10	30	30
Avicel pH 102	58.3	58.3	38.3	57.3	38.3	62.3	37.3	37.3
Ac-Di-sol	7	7	7	7	7	7	7	7
Orange Flavor	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2
Magnesium Stearate	0.5	0.5	0.5	1.5	0.5	1.5	1.5	1.5

Precompression Properties:

Angle of Repose: The Angle of Repose was determined by funnel method. The height of funnel was adjusted from the surface of the graph paper.

The powder was allowed to flow through the funnel on to a graph paper in such a way that the tip of funnel just touches the heap of powder. The diameter of the powder cone was measured, and angle of repose was calculated using the following equation;

$$\tan \theta = 2h/D$$

Where, θ = angle of repose, h = height of the pile, D = diameter of the heap.

Bulk Density: The bulk density was determined by pouring gently 10 gm of powder through a glass funnel into a 50 ml graduated cylinder. The volume occupied by the sample was recorded. The bulk density was calculated as follows:

$$\text{Bulk density } (\rho b) = \text{Weight / Bulk volume}$$

TABLE 7: RELATION BETWEEN ANGLE OF REPOSE AND FLOW OF THE PARTICLES

Angle of repose (θ) (degrees)	Flow
<25	Excellent
25-30	Good
30-40	Passable
>40	Poor

Tapped Density: 10 g of sample was poured gently through a glass funnel into a 50 ml graduated cylinder. The cylinder was tapped from height of 2 inches until a constant volume was obtained. The volume occupied by the sample after

tapping were recorded and tapped density was calculated as follow

Tapped density (ρt) = Weight / Tapped volume

Carr's Index: The compressibility index of powder blend was determined using Carr's compressibility index;

Carr's index = ((ρt – ρb))/(ρt) × 100

Hausner Ratio: Hausner ratio was determined for the characterization of the flow powder blend. Hausner ratio greater than 1.25 is considered to be an indication of poor flowability. The formula used as follows;

Hausner ratio = ρt/ρb

TABLE 8: RELATIONSHIP BETWEEN COMPRESSIBILITY INDEX AND HAUSNER RATIO

Compressibility index (%)	Flow character	Hausner ratio
<10	Excellent	1.00-1.11
11-15	Good	1.12-1.18
16-20	Fair	1.19-1.25
21-25	Passable	1.26-1.34
26-31	Poor	1.35-1.45
32-37	Very poor	1.46-1.59
>38	Very very poor	>1.60

Evaluation of Post Compression Parameters:

General Appearance: General appearance evaluation includes the size of the tablet, shape, color, presence or absence of an odor, taste, surface texture, physical flaws and consistency, and legibility of any identifying marking.

Size and Shape: The size and shape of the tablet can be dimensionally described, monitored, and controlled. Tablet thickness-Tablet thickness is an important characteristic of reproducing appearance and also in counting by using filling equipment.

Some filling equipment utilizes the uniform thickness of the tablets as a counting mechanism. Ten tablets were taken, and their thickness was recorded using a micrometer.

Weight Variation Test: I.P. procedure for Weight Variation test was followed, twenty tablets were taken, and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight.

TABLE 9: LIMIT FOR WEIGHT VARIATION TEST I.P

Average weight of a tablet (mg)	Percentage Difference (+ or -)
Less than 80 mg	10
80mg to 250 mg	7.5
More than 250 mg	5

Tablet Hardness: Hardness of the tablet is defined as the force applied across the diameter of the tablet in order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under the condition of storage transformation and handling before usage depends on its hardness. Hardness of the tablet was determined using a Monsanto Hardness tester.

Friability: It is measured by mechanical strength of tablets. Roche friabilator was used to determine the friability by following procedure. A preweighed tablet was placed in the friabilator. Friabilator consists of a plastic-chamber that revolves at 25 rpm, dropping those tablets at a distance of 6 inches with each revolution. The tablets were rotated in the friabilator for at least 4 min. At the end of test, tablets were dusted and reweighed, the loss in the weight of a tablet is the measure of friability and is expressed in percentage as

% Friability = loss in weight × 100 / Initial weight

Wetting Time: A piece of tissue paper (12 cm × 10.75 cm) folded twice was placed in a small petridish (ID = 6.5 cm) containing 6 ml of Sorenson's buffer pH 6.8. A tablet was put on the paper, and the time for complete wetting was measured. Three trials for each batch and the standard deviation were also determined.

***In-vitro* Disintegration Test:** The test was carried out on 6 tablets using the apparatus specified in I.P. 1996 distilled water at 37 ºC ± 2 ºC was used as a disintegration media and the time in second taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured in seconds.

Assay: Twenty tablets were randomly sampled from each formulation, finely powdered and individually estimated for the assay content after suitable dilution with methanol using a UV-VIS spectrophotometer (UV-1700 Shimadzu) at 258 nm.

***In-vitro* Drug Release Study:** The drug release study for the prepared tablets was carried out using USP XXI Dissolution Test Apparatus-II (Electrolab) paddle method in 900 ml Phosphate buffer pH 6.8 maintained at 37 ± .5 ºC, at 50 rpm. A 5 ml sample was withdrawn at each predetermined time interval. The volume withdrawn at each interval was replaced with fresh 5 ml of fresh dissolution medium. The collected samples were suitably diluted, and absorbance was measured spectrophotometrically at 258 nm. The percentage of PCPM released at various time intervals was calculated and plotted against time. The results shown for dissolution studies are the average of three determinations.

Stability Studies: Accelerated stability studies were carried out to observe the effect of temperature and humidity on tablet formulations as per ICH guidelines by keeping tablet samples at 40 ºC ± 2 ºC in airtight high-density polyethylene bottle for three months, at RH 75 ± 5%. The samples were subjected to physical evaluation, drug content, *in-vitro* release study every month.

RESULTS AND DISCUSSION:

Analytical Method of Prochlorperazine Maleate:

UV Spectrophotometric Method: The linear relationship was evaluated by calculation of the regression line by the method of least squares [12].

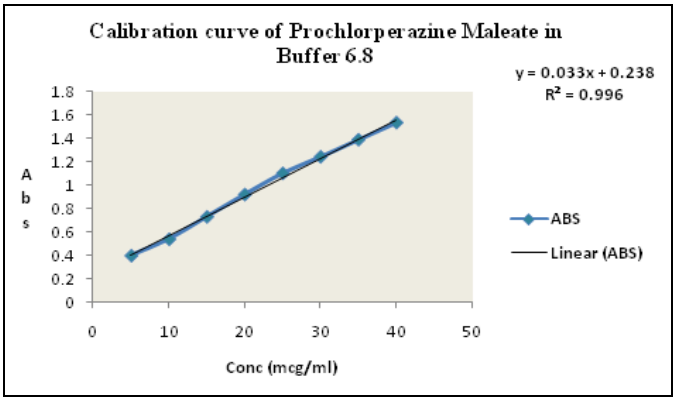

FIG. 1: STANDARD CALIBRATION CURVE OF PROCHLORPERAZINE MALEATE IN BUFFER 6.8

Drug-excipient Compatibility Studies:

Fourier Transform Infrared Spectroscopy (FTIR): Further drug-excipient compatibility study investigated by FTIR spectroscopy. Pure PCPM shows absorption bands around.

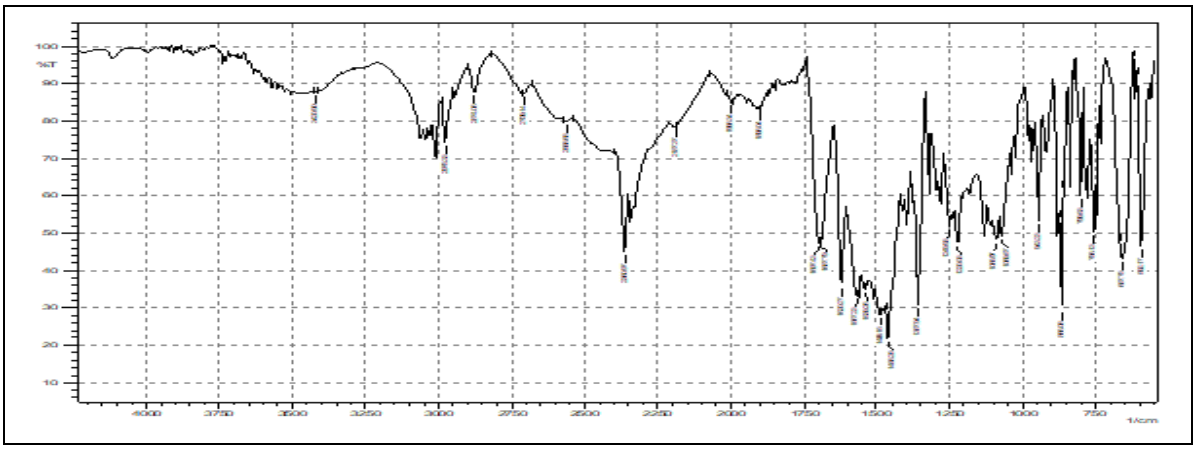

FIG. 2: FTIR OF PURE PROCHLORPERAZINE MALEATE

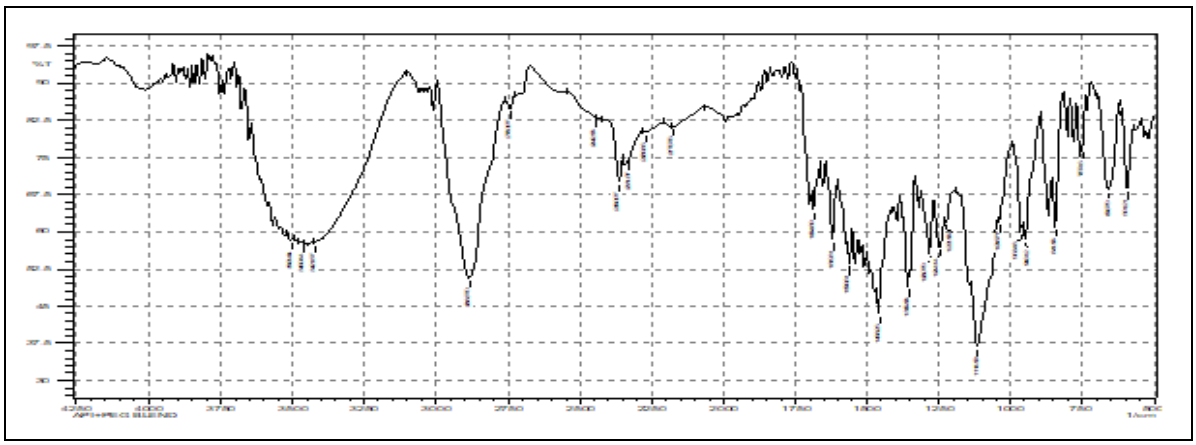

FIG. 3: FTIR OF API+PEG BLEND

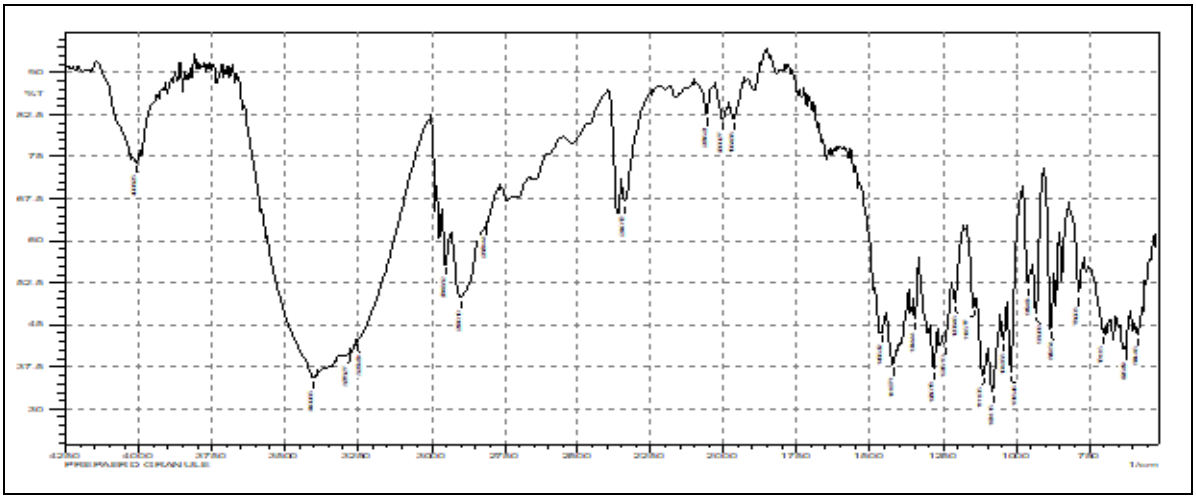

FIG. 4: FTIR OF OPTIMISED F4 FORMULATION

TABLE 10: FTIR OF PCPM

Absorption peak	Functional group
3447.91	Stretching OH group
3058.21	Aromatic CH-stretching
2974.36, 3009.08	Aliphatic CH- Stretching
1700.32,1618.35	Carbonyl group of Acid C=O stretching

API+PEG blend and Optimised formulation F4 IR spectra revealed no considerable change when compared that of the pure drug prove that there is no interaction between drug and excipient.

Differential Scanning Calorimetry (DSC): The DSC thermogram **Fig. 5** of pure PCPM showed a sharp endotherm at 205.7 ºC and optimized Formulation F4 **Fig. 6** showed at 171.1 ºC, which indicated the absence of any interaction between drug and excipients.

Formulation of Sublingual Tablets by Melt Granulation Technique:

Optimization of Blend of PEG 400 and PEG 6000 (Meltable Binder): The optimized PEG blend that possessed a melting point in a range of 37 °C consisted of a 3:7 weight ratio, whereas, a melting point in a range of 35 °C was obtained by using a 2:8 weight ratio (PEG 400: PEG 6000) used for granule preparation.

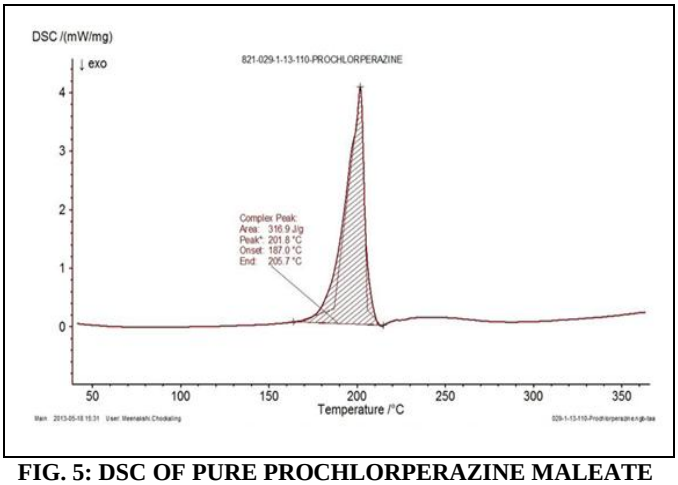

FIG. 5: DSC OF PURE PROCHLORPERAZINE MALEATE

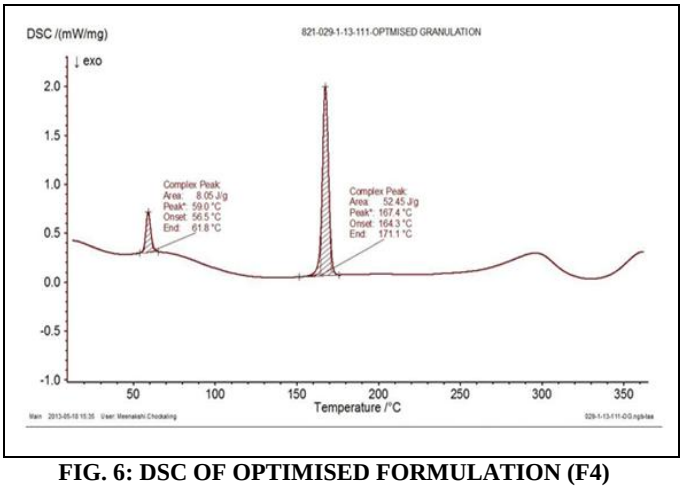

FIG. 6: DSC OF OPTIMISED FORMULATION (F4)

Optimization of Sugar: PEG Ratios: High concentration of PEG blend in the powder led to stickiness and softness of the mixture due to the low melting point (37 °C) of the PEG blend. The presence of a mixture of low and high melting point (different melting points) polyethylene glycols has an effect on tablet hardness. As the percent of the low melting point polyethylene glycol increased in the tablet formulation, the tablet hardness was reduced. The larger the percentage of polyethylene glycol 400 present in the PEG blend 2:8, which was used to prepare the tablet resulted in less hardness leading to breaking of the tablet. The presence of PEG blend 2 with its low melting point (35 °C), resulted in the softness of the tablets, and hence their low hardness and high friability.

TABLE 11: TABLET CONTAINING 2:8 (PEG400: PEG 6000) RATIO

Formulation Code ↓	Ratios (Sugar: PEG blend)	Properties
A	1:1	Surface texture not good
B	2:1	Very sticky, picking, tablet not formed
C	3:1	Sticky, tablet was not formed
D	4:1	Tablet was not formed
E	5:1	Tablet was not formed

Study of Compressibility of Prepared Meltable Granules: Granules obtained by optimization of PEG blend and sugar: PEG ratios.

The granules were mixed with other tablet additives geometrically. The tablet properties of PEG ratios 2:8 and 3:7, as shown in **Table 11** and **12**.

TABLE 12: TABLET CONTAINING 3:7 (PEG 400: PEG 6000) RATIO

Formulation code ↓	Ratios (Sugar: PEG blend)	Tablet properties	Hardness (Kg/cm^2)	Friability (%)	Disintegration time (min)
A	1:1	Sticky, tablet was not formed	-	-	-
B	2:1	Sticky, tablet was not formed	-	-	-
C	3:1	Tablet formed, white appearance & smooth.	1	0.25	2
D	4:1	Tablet formed, off white appearance & rough	0.5	0.15	1.5
E	5:1	Tablet formed .off white appearance & rough.	1	0.30	2

From the above observation table, it was observed that the 3:7 PEG ratio shows better tableting properties than a 2:8 ratio. When (PEG 400 & PEG 6000) were taken in ratio 2:8, the powder mass was very sticky, and tablets were difficult to compress. From the results, it was observed that when 3:7 PEG blend was used, the 3:1, 4:1, and 5:1 ratios of Sugar: PEG formed the tablet with desirable properties. Among all the ratios, 3:1 showed good tableting properties.

Preparation of Granules by using Meltable Binders: Granules prepared by PEG blend and Gelucire used as meltable binder was obtained.

Evaluation of Granules:

Effect of Meltable Binders on *In-vitro* Dissolution Profile of PCPM: *In-vitro* dissolution profiles of the granules prepared by melt granulation technique were compared with that of the pure drug. The dissolution rate of pure PCPM was very low. The *in-vitro* dissolution rate of all prepared granules was higher as compared to the pure drug.

Granules containing PEG blend as a binder, a significant improvement was observed in the dissolution rate as compared to the pure drug. These results show that melt granulation may prove to be a useful technique to improve the dissolution rate of PCPM

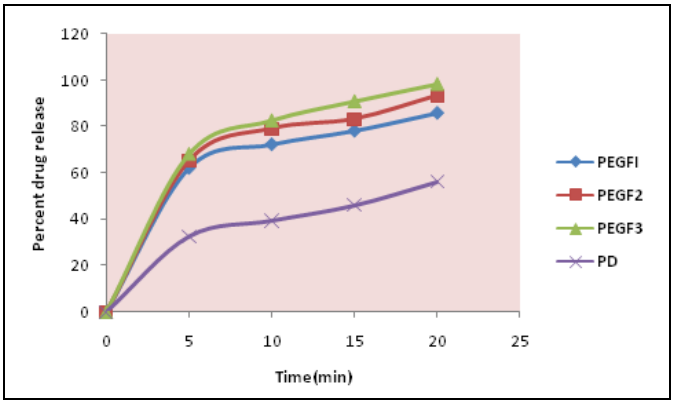

FIG. 7: *IN-VITRO* DISSOLUTION PROFILE OF PEGF1 (30% SUGAR: PEG RATIO + 58.8% AVICEL), PEGF2 (35% SUGAR: PEG RATIO + 53.8% AVICEL) AND PEGF3 (40% SUGAR: PEG RATIO + 48.8% AVICEL) GRANULATES IN COMPARISON WITH PURE PCPM

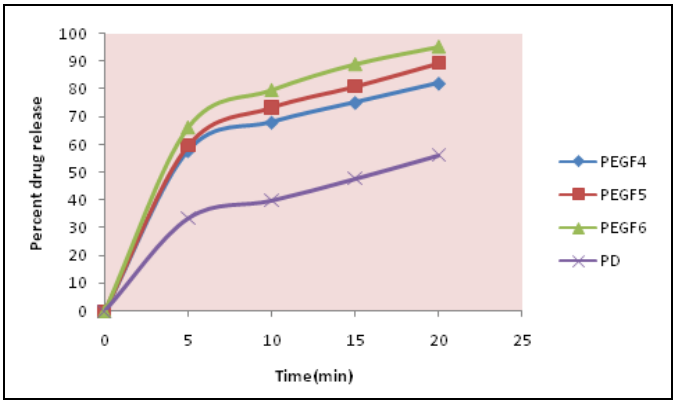

FIG. 8: *IN-VITRO* DISSOLUTION PROFILE OF PEGF4 (30% SUGAR: PEG RATIO + 58.8% LACTOSE), PEGF5 (35% SUGAR: PEG RATIO + 53.8% LACTOSE) AND PEGF6 (40% SUGAR: PEG RATIO + 48.8% LACTOSE) GRANULATES IN COMPARISON WITH PURE PCPM

Above figure shows that the formulation PEGF3 containing PEG blend and Avicel as a diluent gives 98.22% drug release within 20 min as compared to PEGF1 and PEGF2. It was also observed that formulation PEGF4 to PEGF6 containing PEG blend and lactose as diluents gives a 95.15% drug release within 20 min. Therefore it was concluded that Avicel & Lactose as diluents in the formulation not influencing drug release significantly.

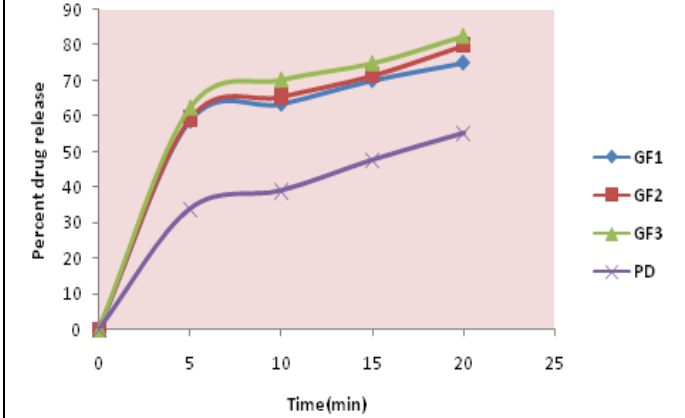

FIG. 9: *IN-VITRO* DISSOLUTION PROFILE OF GF1 (30% GELUCIRE+ 58.8% AVICEL), GF2 (35% GELUCIRE + 53.8% AVICEL) AND GF3 (40% GELUCIRE + 48.8% AVICEL) GRANULATES IN COMPARISON WITH PURE PCPM

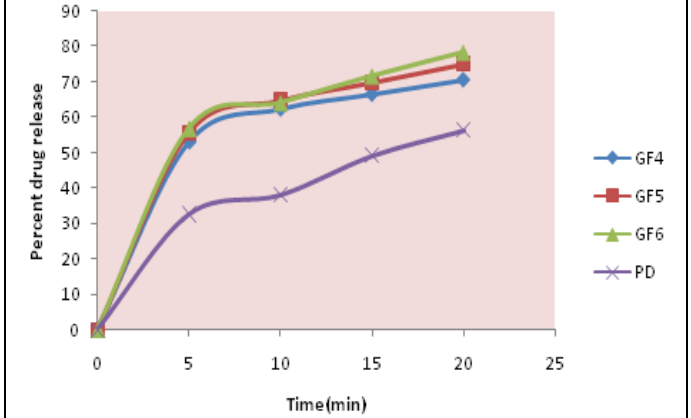

FIG. 10: *IN-VITRO* DISSOLUTION PROFILE OF GF4 (30% GELUCIRE+ 58.8% LACTOSE), GF5 (35% GELUCIRE+ 53.8% LACTOSE) AND GF6 (40% GELUCIRE+ 48.8% LACTOSE) GRANULATES IN COMPARISON WITH PURE PCPM

The above figure shows that there was an improvement in the dissolution profile of pure drug when Gelucire was used as a meltable binder in various percentage (85.22% in 20 min from formulation GF3). It was also observed from **Fig. 9** and **Fig. 10** that type of diluents (*i.e.*, Avicel & Lactose) had no effect on the dissolution profile of drug in the presence of Gelucire. But it is important to note that PEG blend was superior to Gelucire in improving dissolution profile of PCPM (98.22% in 20 min). Therefore, the PEG blend was chosen for the preparation of sublingual tablets of PCPM.

Preparation of Tablets by using Gelucire (Hydrophilic Meltable Binder): After the evaluation of tablets prepared using Gelucire, it was observed that the tablet disintegrates range in 10 min and has hardness was 1 kg/cm^2. Whereas tablets prepared using PEG blend as a meltable binder disintegrated within 1.5 to 2 min.

This may be because Gelucire has formed closed packing of granules during compression than PEG. Gelucire gives less drug release as well as takes more disintegration time with unacceptable hardness as compared to the PEG blend. Gelucire attributed the undesirable results. Therefore, PEG was chosen as a meltable binder for further process.

Effect of Various Excipients on Tabletting Properties:

TABLE 13: EFFECT OF VARIOUS EXCIPIENTS ON TABLETTING PROPERTIES

Formulations	Hardness (kg/cm$^{2)}$	Friability (%)	Disintegration (sec)
FP1	0.3	0.15	300
FP2	0.3	0.40	270
FP3	0.35	0.25	240
FP4	0.35	0.30	300
FP5	1.5	0.28	20
FP6	1	0.30	20
FP7	1	0.20	600
FP8	1	0.22	564

From **Table 13**, it can be observed that formulation FP1 to FP4 (Tablets containing Natrosol) shows less hardness and slower disintegration as compared to formulation FP5 and FP6 (Tablets containing Prosolv). It can also be seen that formulations FP7 and FP8 are slow disintegrating as compared to formulation FP5 and FP6 (Tablets containing Granular Mannitol). Therefore, we selected Prosolv and granular mannitol in the final tablet formulation as excipients.

Optimised Tablet Formulation: Optimised Formulations F1 to F8 were subjected to pre-compression parameters and after compression by

using 8 mm round flat punches on 12 stations rotary tablet machine. Tablet evaluated for post-compression parameters.

Pre-compression Properties: Table 13 shows the results of an evaluation of precompression properties. Bulk density of all the formulations was found to be between 0.45 ± 0.0010 to 0.64 ± 0.03 g/cc, tapped density between 0.54 ± 0.01 to 0.72 ± 0.03 g/cc, Carr's index in the range 10.76 ± 0.1 to 19.44 ± 0.26 %.

Hausner ratio between 1.12 ± 0.11 to 1.24 ± 0.25 and angle of repose was found to be in the range 29.14 ± 0.17 to 33.55 ± 0.25 indicating fair to good flow properties for all the powder mixtures.

TABLE 14: PRECOMPRESSION PROPERTIES OF POWDER

Formulations	Angle of Repose (θ °)	Bulk density (kg/cm^2)	Tapped density (kg/cm^2)	Carr's Index	Hausner's ratio
F1	30.23 (±0.22)	0.52 (±0.001)	0.64 (±0.01)	16.66 ± 0.14	1.23 ± 0.35
F2	33.14 (±0.21)	0.59 (±0.03)	0.69 (±0.02)	14.49 ± 0.23	1.16 ± 0.2
F3	29.14 (±0.17)	0.45 (±0.001)	0.54 (±0.01)	16.66 ± 0.26	1.23 ± 0.3
F4	30.65 (±0.30)	0.58 (±0.02)	0.65 (±0.02)	10.76 ± 0.1	1.12 ± 0.05
F5	33.41 (±0.28)	0.63 (±0.01)	0.73 (±0.07)	13.69 ± 0.09	1.15 ± 0.01
F6	32.56 (±0.20)	0.64 (±0.03)	0.72 (±0.01)	11.11 ± 0.12	1.12 ± 0.1
F7	32.44 (±0.35)	0.60 (±0.019)	0.71 (±0.04)	15.49 ± 0.25	1.18 ± 0.19
F8	33.55 (±0.25)	0.58 (±0.02)	0.72 (±0.03)	19.44 ± 0.26	1.24 ± 0.25

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

Evaluation of Post Compression Parameters of PCPM Tablets: After evaluation of pre-compression parameters, tablets were compressed using the Rotary 12 station tablet machine (CEMACH). Compressed tablets were then evaluated for physical parameters like thickness, hardness, friability, weight variation, and drug content. All the formulations showed uniform thickness and diameter in **Table 14**. In a weight variation test, the pharmacopoeial limit for the percentage deviation for the tablets of 80 mg to 250 mg is ± 7.5%. The average percentage deviation of all tablet formulations was found to be within the limit, and hence all formulations passed the test for uniformity of weight as per official requirements. The hardness of all the formulations was between 0.5 to 2 kg/cm^2. The percentage friability for all the formulations was below 1%, indicating that the friability is within the prescribed limits. The disintegration time of the tablets varied from 20 to143 sec.

TABLE 15: POST-COMPRESSION PARAMETERS OF TABLET

Formulation	Weight Variation (gm)	Thickness (mm)	Hardness (Kg/cm^2)	Friability (%)	Wetting Time (sec)	Disintegration Time (sec)
F1	0.120 (±1.5)	3.40 (±0.2)	0.5 (±0.06)	0.573 (±0.01)	2 (±0.1)	8 (±0.01)
F2	0.120 (±2.2)	3.44 (±0.25)	1.5 (±0.01)	0.25 (±0.01)	20 (±0.6)	143 (±15.25)
F3	0.119 (±2.6)	3.41(±0.06)	1 (±0.02)	0.20 (±0.02)	32 (±0.15)	190 (±24.10)
F4	0.120 (±2.45)	3.45 (±0.01)	2 (±0.06)	0.1 (±0.01)	18 (±0.02)	122 (±43.31)
F5	0.119 (±4.5)	3.50 (±0.02)	1 (±0.01)	0.6 (±0.025)	9 (±0.06)	20 (±0.75)
F6	0.120 (±5.1)	3.44 (±0.1)	1 (±0.04)	0.34 (±0.01)	10 (±1.5)	38 (±4.54)
F7	0.119 (±2.5)	3.46 (±0.11)	1.5 (±0.02)	0.6 (±0.05)	18.5 (±0.5)	120 (±45.5)
F8	0.119 (±1.25)	3.44 (±0.02)	1 (±0.01)	0.1 (±0.01)	20 (±0.01)	141 (±20.56)

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

From the above-tabulated results, it was possible to reject the following formulations based on unacceptable Hardness: F1, F3, F5, F6, and F8. The remaining formulations had acceptable friability. Final formulations were chosen on the basis of acceptable hardness and disintegration time. Tablet formulations F1 & F5 show desirable disintegration properties, but resulting tablets were not having desirable hardness and were not handlable. Therefore, formulations F2, F4 & F7 were chosen to have required hardness for further evaluations. Consequently, F2 (containing 3:1 sugar: PEG ratio), F4 (containing 3:0.25 ratio) and F7 (containing 3:0.25 ratio) were chosen as final formulations and prepared batches of 100 tablets each, and the results of their evaluation are listed in the following **Table 16**.

TABLE 16: EVALUATION PARAMETERS OF OPTIMISED FORMULATIONS

Formulation ⟶	F2	F4	F7
Visual Examination		White cylindrical tablets with orange odor	
Thickness (mm)	3.40 (±0.02)	3.38 (±0.03)	3.42 (±0.01)
Average weigh (gm)	0.119 (±1.5)	0.120 (±1.2)	0.119 (±1.25)
Drug Content (%)	96.36 (±0.45)	98.69 (±0.55)	95.35 (±0.86)

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

***In-vitro* Drug Release Studies:** The *in-vitro* dissolution profiles of Optimized PCPM Tablet prepared by melt granulation technique were compared with that of pure drug. The dissolution rate of pure PCPM was very low.

The *in-vitro* dissolution rate of all prepared tablets was higher as compared to the pure drug, but among the optimized formulations F2, F4, F7, the formulation F4 shows a 95.16% drug release in 20 min.

TABLE 17: RESULT SHOWING DRUG RELEASE OF FORMULATIONS F2, F4, F7 AND PURE DRUG

Time (Min)	%CDR (F2)	%CDR (F4)	%CDR (F7)	%CDR (PD)
0	0	0	0	0
5	60.5 ± 0.65	65.06 ± 0.1	58.22 ± 0.06	30.45 ± 0.25
10	75.85 ± 0.02	81.15 ± 0.05	65.09 ± 0.55	45.99 ± 0.57
15	80.20 ± 0.35	89.10 ± 0.89	75.25 ± 0.98	52.10 ± 0.45
20	85.10 ± 0.12	95.16 ± 0.77	80.44 ± 0.19	60.25 ± 0.39

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

The increase in dissolution rate could be attributed to the higher hydrophilic character of the system due to the presence of water-soluble carriers (PEG), and that part of the drug dissolves in the binder.

Stability Studies: Accelerated stability studies were carried out as per ICH guidelines. Formulation (F4) did not show any physical changes during the study period. Drug content was found to be more than 98% at the end of 3 months in accelerated conditions. This indicates that the prepared tablets (F4) are stable at accelerated storage conditions.

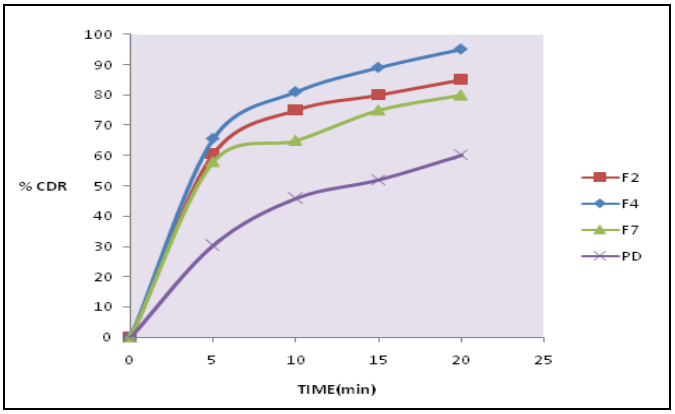

FIG. 11: GRAPH SHOWING %CDR OF FORMULATIONS F2, F4, F7 AND PURE DRUG

TABLE 18: STABILITY STUDY OF OPTIMISED F4 PCPM SUBLINGUAL TABLETS

Storage condition→	Room Temperature	40 ºC / 75% RH		
Period→	Initial	1 Month	2 Months	3 Months
Formulations →	F4	F4	F4	F4
Parameters↓	**Observations**			
Physical Appearance	White	White	White	White
Hardness (kg)	2 ± 0.06	2 ± 0.08	1.8 ± 0.22	1.8 ± 0.22
D.T	122 ± 43.31	122 ± 0.64	117 ± 0.64	118 ± 0.21
Drug content (%)	98.69 ± 0.89	98.32 ± 0.54	98.20 ± 0.75	98.0 ± 0.45
Dissolution	95.16 ± 0.35	94.7 ± 0.89	93.25 ± 0.12	90 ± 0.29

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

CONCLUSION: Sublingual tablets are intended to dissolve slowly in the oral cavity within 1 to 10 min. Their success lies in their ability to allow the absorption of the major portion of the drug through the oral mucosa. The use of the sublingual route allows for improving the drug bioavailability due to avoiding the first-pass effect and prevention of drug exposure to the gastrointestinal tract secretions and the rapid onset of action. Improving the dissolution characteristics of poorly water-soluble drugs is important to achieve better bioavailability and reduced side effects. The Melt granulation technique is an important tool in this direction. PCPM is practically insoluble in the

water, thereby shows poor bioavailability and first-pass hepatic metabolism when administered orally. Granules produced by melt granulation were subjected to drug excipient compatibility study was carried out using Fourier transform infrared spectroscopy (FTIR) and Differential scanning calorimetry (DSC). It was found that there was no interaction between drug and excipient.

Thus the Melt granulation technique was employed to enhance the solubility, thereby bioavailability of PCPM. PEG blend (PEG 6000 + 400) and Gelucire as hydrophilic polymers were used to improve the solubility and dissolution profile of PCPM. But when *in-vitro* dissolution profiles of granules prepared using PEG & Gelucire, Gelucire showed less significant drug release as compared to PEG blend; therefore, PEG blend was used as a hydrophilic carrier to prepare the tablet. Granules were prepared with Drugs to different PEG: sugar weight ratio.

Sucrose is hygroscopic, especially at elevated temperatures and at high humidity. Mannitol, however, has less hygroscopicity and reduces disintegration time, yet possess low compressibility and results in a soft tablet. Granulation of mannitol improves its compressibility. Also, the inclusion of Prosolv® into formulations resulted in further improvement in flow properties. The presence of a mixture of low and high melting point PEG (polyethylene glycols) has an effect on tablet hardness. As the percent of the low melting point polyethylene glycol increased in the tablet formulation, the tablet hardness was reduced. The larger the percentage of polyethylene glycol 400 present in the PEG blend 2 (which was used to prepare the formulations upon compression), softer tablets were obtained in **Table 11**.

The use of PEG 6000 results in prolongation of the disintegration time of tablets due to its binding effects. The higher the amount of polyethylene glycol 6000 incorporated in the tablet formulation, the longer the disintegration time. Thus, as the percent of PEG blend in the sugar / PEG mixture decreased from (3:1sugar: PEG) to (3:0.25), the disintegration time decreased from 143 to 122 s. The impairment of the flow properties of the powders was due to the high concentration of included PEG blend in the powder (3:1 granular mannitol: PEG, respectively). Incorporation of high concentration of PEG blend in the powder mixture resulted in the sticky and soft mixture, difficult to compress. This may be due to the low melting point (37 °C) of the PEG blend. Thus, hardness and disintegration time of the tablet are functions of the amount and melting point of the PEG used as a binder.

The use of Avicel PH 102 improves the flow properties of powders due to its granular form, despite its low compressibility resulted from its large particles. This poor compressibility is overcome by the use of Prosolv®, which has got better flow and compressibility properties, compared to a physical mixture of microcrystalline cellulose and silicon dioxide.

Prosolv® has improved powder flow properties compared to microcrystalline cellulose (Avicel), thus explaining the lower values for both the angle of repose and the percent compressibility. *In-vitro* release studies in pH 6.8 phosphate buffer demonstrate the faster release of PCPM from Tablet than pure drug. Tablet formulation F4 showed the highest drug release in the *in-vitro* dissolution studies 95.16% in 20 min compared to pure drug release 60.25% in 20 min.

In conclusion, the adopted melt granulation technique for the preparation of sublingual tablets proved to be effective in enhancing the dissolution rate of PCPM. The presence of Hydrophilic meltable binder PEG in the formulation favored the rapid uptake of drug sublingually, avoiding its loss by the first-pass effect. Melt granulation technique was found to be less time-consuming in terms of time & energy as compared to other conventional granulation methods. Therefore it is essential to mention that the present technique has an ability to improve solubility & bioavailability of poorly soluble drugs as well as has a substantial commercial potential.

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CONFLICTS OF INTEREST: The authors declare that they have no conflicts of interest.

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