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FORMULATION AND EVALUATION OF ORODISPERSIBLE TABLETS OF APREPITANT

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Abstract:

The present research is directed towards the development of Formulation and evaluation of orodispersible tablets of taste masked Aprepitant to improve thebioavailability of Aprepitant which shows 70%. The Oral Dispersible Tablets (ODTs) of various batches were prepared by using various concentrations of various super disintegrants like sodium starch glycolate, crospovidone and croscarmellose sodium by direct compression method. In the present work nine formulations were prepared using mannitol as diluent, aspartame as sweetener, and talc as glidant. All the prepared ODT formulations were evaluated for physical characteristics, disintegration, In Vitro dissolution and stability study. The hardness of formulations (F1-F9) was in the range of 3.13 – 3.4 Kg/cm^2 indicating good mechanical strength and the thickness of formulations were in the range of 5.13 – 5.72 mm. The weight variation and the friability were found within the official limits. The In Vitro dispersion time of all the formulation was done and observed thatthere is decrease in the In Vitro dispersion time with the increase in the concentration of superdisintegrant. In Vitro dissolution study of all the formulations was carried out for 15 minand according to results formulation F3 was found as the best formulation, which showed 99.5% drug release at the end of 15 min. The selected formulation was subjected for the short-term stability study for 60 days and the hardness, taste, friability, drug content and disintegration were observed and found no significant change in the results.

Keywords: *Orodispersible tablets, Aprepitant, Eudragit E100, Mass extrusion method, Superdisintegrant, in-vitro dissolution study.*

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INTRODUCTION

An ideal dosage regimen in the drug therapy of any disease is the one, which immediately attains the desire therapeutics concentration of drug in plasma (or at the site of action) and maintains it constant for the entire duration of treatment [1]. Drugs are frequently taken by oral administration, although a few drugs taken orally are intended to be dissolved within the mouth, majority of drugs taken orally are swallowed. Compared with alternate routes, the oral route of drug administration is the most popular and has been successfully used for conventional delivery of drug. It is considered as most natural, convenient means of administering drugs [2]. Oral Dispersible Tablet is an innovative tablet technology where the dosage form containing active pharmaceutical ingredients disintegrates rapidly, usually in a matter of seconds, without the need for water, providing optimal convenience to the patient [3]. The basic methods used to prepare solid dispersions are Melting method or fusion method, Solvent evaporation method, Kneading method. supercritical Fluid Process [4,5]. Mechanical strength, disintegration time, Taste masking, are the different challenges to develop oral dispersible tablet [6]. Shape and Color, Uniformity of Thickness) Hardness test, Friability test, Content uniformity test etc. are the post-compression evaluation parameters for formulation of tablet.

The basic approach to the development of fast dissolving tablets (FDT) is the use of super disintegrants. ODT shows less sensitivity to environmental conditions and temperature [7,8]. It produces quick onset of action due to rapid disintegration, dissolution and absorption of tablets. Freeze Drying, Tablet Molding, Spray drying are the conventional technologies for fast dissolving tablet [9]. Few properties of fast dissolving tablets such as no bitter taste, dose lower than 20mg, small to moderate molecular weight, good stability in water and saliva. Aprepitant is the nonpeptide antagonist of neurokinin 1(NK1).

The present research is directed towards the development of Formulation and evaluation of orodispersible tablets of taste masked Aprepitant to improve thebioavailability of Aprepitant which shows 70% [10]. As the Aprepitant is bitter in taste, taste masking has been done by using a polymer Eudragit E100 which is a cationic copolymer based on dimethylaminomethyl methacrylate, butyl methacrylate and methyl methacrylate by mass extrusion method. The ODTs of various batches were prepared by using various concentrations of various super disintegrants like sodium starch glycolate, crospovidone and croscarmellose sodium by direct compression method [11].

MATERIALS AND METHODS:

Materials

Aprepitant was obtained from Dr. Reddy's Laboratories Ltd. (Hyderabad, Telangana, India). Eudragit E100 was purchased from Sigma Aldrich. Sodium starch glycolate, Croscarmellose sodium, Cross povidone was purchased from SD Fine Chemicals

Methods

PREFORMULATION STUDY:

Melting point:

Using melting point equipment, the drug's melting point was identified. This was measured against the drug's official melting point value.

PREPARATION OF DRUG POLYMER COMPLEX (DPC):

Dissimilar proportions of medication and Eudragit E100 were blended to create the drug polymer complex (DPC). The drug and polymer combination were gradually added while being continuously stirred (at a speed of 600 rpm) into a 500ml glass beaker containing 10% ethanol until a gel shaped. On a polycarbonate sheet, the gel was physically pushed out using a syringe. After the gel was extruded, ethanol was allowed to evaporate at ambient temperature for an entire night before being vacuum dried at -700 mm of Hg at 350°C for six hours [12]. After that, the sample was pulverised in a mortar and pestle and hoover dried once more below the aforesaid circumstances to guarantee passable solvent exclusion. Further research was conducted using the prepared taste-masked granule

CHARACTERIZATION OF DPC (Drug polymer complex):

Drug content:

DPC equal to 75 mg of drug was agitated in 100 ml of 0.1 N HCl for 60 minutes with a magnetic stirrer until the full amount of medicine leaked out of the complex [13]. The solution was then sifted with whatman filter paper. Additionally, the drug content of the solution was assessed spectrophotometrically at 315 nm after being diluted with 0.1 N HCl.

***In Vitro* taste evaluation:**

By calculating the medication release from the compound into simulated salivary fluid (SSF) (pH 6.8), it was possible to anticipate the release of the medication in human saliva. DPC was added to 10 ml screw-capped bottles of SSF and shaken for 60 seconds at 50 revolutions per minute. This is equivalent to 10 mg of aprepitant (or a dose of 75 mg).

At 315 nm, the amount of medication released was measured [14].

PREPARATION OF TABLETS:
The ODT preparation used an optimized lot of medicine polymer complex equating to 75 mg of aprepitant. Aspartame, mannitol, crospovidone, and sodium carboxymethyl cellulose were each weighed and put through a #40 mesh filter [15]. After correctly combining the above-mentioned sifting excipients with the optimised DPC and mixing for three minutes, mint flavoring was added. Lastly, talc and magnesium stearate were additional and carefully mixed for 2 minutes. Using a 10 mm concave punch, the powder mixture was compacted.

FORMULATION OF APREPITANT ODTs:

Table No: 1 Preparation of Aprepitant ODTs

Components for one tablet (mg)	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
DPC (equal to 75mg of Aprepitant)	370	370	370	370	370	370	370	370	370
Mannitol	50	45	40	50	45	40	50	45	40
Crosspovidone	9	14	22	-	-	-	-	-	-
CCS	-	-	-	9	14	22	-	-	-
SSG	-	-	-	-	-	-	9	14	22
Aspartame	5	5	5	5	5	5	5	5	5
Mint Flavour	3	3	3	3	3	3	3	3	3
Magnesium stearate	7	7	7	7	7	7	7	7	7
Talc	5	5	5	5	5	5	5	5	5
Total mass	450	450	450	450	450	450	450	450	450

DPC – Drug Polymer Complex

PRE-COMPRESSION STUDIES
Bulk density:
The poured density is another name for it. It is the proportion of the powder's overall mass to its volume in its bulk. It was calculated by adding 20 g of powder (accepted over standard screen # 20) to a 100 ml measure, and recording the early volume [16].

Db = M/ Vb
Where,
M is the mass of powder
Vb is the majority volume of the powder.

Tapped density:
It is determined by dividing the powder's total mass by its tapped volume. The powder was tapped 750 times to determine its volume, and if there was a difference of less than 2% between the two volumes, the difference was documented [17]. If it is higher than 2%, tapping is repeated for an additional 1250 times, and the volume of taps is logged. In a bulk density apparatus, tapping was continual till the variance among following capacities was less than 2%. It is articulated in g/ml and is given by

Dt = M / Vt
Where,
M is the mass of powder
Vt is the tapped volume of the powder.

Angle of repose (θ):
The funnel was permitted to empty into a container as the powder combination was allowed to flow through [18]. It was carefully observed that the powder particles passed through the funnel's sides and rolled on top of one another.

$\tan(\theta) = h / r$ $\theta = \tan^{-1}(h / r)$

Carr's index (or) % compressibility:
It is stated in percentage and is given

$$I = \frac{Dt - Db}{Dt} \times 100$$

Hausner ratio:
Hausner ratio is a secondary guide of ease of powder flow.

$$\text{Hausner ratio} = \frac{D_t}{D_b}$$

Where,
Dt is the tapped density.
Db is the wholesale density
Lesser hausner ratio (<1.25) specifies improved flow properties than higher ones (>1.25).

POST COMPRESSION STUDIES OF TABLETS:
Description:
General appearance of tablets, including its size, shape, and colour. Consumer acceptability is a requirement, and physical risks that could occur when storing it could occur. It should be easily linked with the description [19].

Weight variation:
20 tablets should be weighed individually to get the average weight. The number of individual weights that differ from the average weight by more than two [20].

Thickness:
Vernier callipers were used to gauge the thickness of ten different tablets.

Hardness:
Using a Monsanto tablet tester, the hardness is determined. The unit of measurement is kg/cm2

where,
Wb is weight of tablet earlier water absorption
Wa is weight of tablet next water absorption.

In Vitro dispersion time:
The amount of time needed for a tablet to completely dissolve in 10 ml of SSF (phosphate buffer solution), pH 6.8, at 37±0.5 ºC, was measured [24].

In Vitro drug release:
A triple in vitro dissolution test was performed using USP Type II (paddle type) equipment. As the dissolution media, 900 ml of SGF (0.1N HCl) was utilised, and the paddle was revolved at 50 rpm for an hour at a temperature of 370C. Every time a sampling interval was completed, 0.1N HCl was added in its stead. At 315 nm, the samples are then

Friability:
The "Electro Lab Friabilator" was cast-off to measure the friability of each batch [21]. Five preweighed tablets were rotated at 25 rpm for four minutes, then the weight loss was calculated as a percentage.

$$F = \frac{\text{Winitial - Wfinal}}{\text{Winitial}} \times 100$$

Wetting time:
A part of tissue paper that had been doubled twice was put in a Petri dish with an interior diameter of 6.5 cm and 6 ml of water that contained the water-soluble stain eosin. The drug was positioned on the paper, and the amount of time it took for the tablet to get fully wet was counted in seconds. For each formulation, this has been done three times to obtain an exact number.

Modified disintegration test:
The conventional disintegration test procedure for these dose forms has a number of limitations and is inadequate for evaluating extremely quick disintegration times. Because disintegration is essential even in the nonappearance of water, the ODT disintegration time needs to be adjusted. As a result, the test should mimic salivary disintegration [22]. After being carefully positioned in the petridish's centre, the time it took for the tablet to wholly fragment into small particles was noted.

Water absorption Ratio:
A tissue paper piece that had been folded twice was put in a little Petri dish with 6 ml of water. The total of period essential for the paper to become fully wet was noted on a tablet when it was placed on the paper. The moist tablet was then weighed [23].

R=10(wa/wb)
spectrophotometrically examined [25].

Content uniformity test:
Standard solution: Make a solution of Aprepitant in water taking a identified concentration of about 0.9 µg/ml.

Sample solution: From the prepared batch, 20 tablets were chosen at random and ground into a fine powder. The weight of the pill in powder form was taken, dissolved in a beaker with a tiny amount of water, and shaken for a while. Filter the solution into a 500 ml volumetric flask, then add water to fill the remaining space [26]. Add 1 ml of this solution to a 100 ml volumetric flask, then add water, take the absorbance at 315 nm.

Stability study:
Six months of accelerated stability testing should be conducted at 400C and 75% RH. At 30 ºC and 65%RH, stability testing under intermediate storage conditions should be performed [27].

RESULTS AND DISCUSSION:

Determination of melting point of Aprepitant:
By using the capillary method, the melting point of aprepitant was discovered to be 132.7 ºC, which is within the range allowed by the legal regulations.

Physical compatibility studies:
There was no alteration in physical description, the investigation shows that the medication, polymer, and other excipients were actually well-matched with one another.

Table 2:Physical compatibility studies of medication and excipients

S.No	Medication + Excipients	Description at initial day	RT, 35±2^{0}C/65±5% RH IN days		
			10th	20th	30th
1.	NZ	Off white to brown crystalline powder	NC	NC	NC
2.	NZ + CP	Off white to creamy powder			
3.	NZ + CCS	Off white to yellow powder			
4.	NZ + SSG	Off white to yellow powder			
5.	NZ + ALL	Off white to yellow free flowing powder			

NZ – Aprepitant, **CP** – Crosspovidone, **CCS –** Croscarmellose sodium, **SSG –** Sodium starch glycolate,**NC** – No change.

In Vitro taste evaluation:

Table 3: Dissimilar Drug-Eudragit E100 concentrations' effects

Drug- polymer ratio	% Drug content*	%Drug dissolved inSSF*	Taste
1:1	97.98±0.38	0.78±0.08	Bitter
1:2	99.08±0.42	0.58±0.05	
1:3	99.02±0.4	0.4±0.04	Slightly bitter
1:4	98.96±0.22	0.08±0.02	No bitter
1:5	98.98±0.08	ND	

* Outcomes are the mean of three observations ± SD,ND – Not detectable

PRE-COMPRESSION STUDIES:

Bulk density:
The bulk density was discovered to be amid 0.5 and 0.522 g/ml.

Tapped density:
The density of the tapped material ranged from 0.583 to 0.598 g/cm3

Compressibility index:
It was found to be in the vicinity of 12.35 - 13.58%, indicating that the preparations have good flow properties.

Hausner ratio:
The formulation powders had improved flow properties, as evidenced by the fact that it ranged between 1.2 and 1.18.

Angle of repose (θ):
The results, which range from 21.8 to 23.27, show that the powders have sufficient flow characteristics.

Table 4: Pre compression data of all preparations

Formulation	Bulk density* g/ml	Tapped density*g/ cm^3	Compressibility index*	Hausner ratio*	Angle of repose (□)*
F1	0.48±0.12	0.58±0.08	13.08±0.08	1.08±0.04	21.4±0.30
F2	0.49±0.22	0.56±0.20	12.96±0.08	1.08±0.03	23.9±0.20
F3	0.60±0.18	0.64±0.18	13.06±0.06	1.12±0.06	26.9±0.18
F4	0.48±0.30	0.58±0.18	14.02±0.09	1.08±0.05	23.9±0.09
F5	0.58±0.18	0.7±0.18	13.10±0.08	1.08±0.03	24.1±0.20
F6	0.62±0.18	0.70±0.08	13.40±0.08	1.08±0.04	25.8±0.30
F7	0.48±0.08	0.58±0.20	13.52±0.08	1.2±0.08	23.9±0.18
F8	0.49±0.20	0.6±0.20	14.02±0.08	1.08±0.10	24.8±0.20
F9	0.61±0.08	0.72±0.08	14.06±0.08	1.02±0.04	25.9±0.18

* Average± SD

POST COMPRESSION STUDIES:

Weight variation:

Table No.12 shows the results of the evaluation of prepared tablets for weight variation. Per the monograph, the weight's percentage deviance was within 5%

Hardness:

The tablets' hardness was determined to be between 3.13 and 3.4 Kg/cm^2, which indicated that the concentration of superdisintegrants was not impacted by the tablets' hardness.

Thickness:

The thickness of the tablet, which was discovered to be between 5.13 and 5.72 mm, is adequate for receiving and packing.

Friability:

The test was established that the friability of the tablet ranged from 0.447 to 0.493%.

Table 5: Post compression constraints of all preparations

Formulation	Average weight variation*	Hardness* (Kg/cm^2)	Thickness* (mm)	Friability* (%)
F1	449±0.08	2.98±0.30	4.98±0.54	0.39±0.10
F2	452±0.14	3.28±0.28	5.38±0.04	0.39±0.06
F3	450±0.20	3.26±0.40	5.68±0.04	0.42±0.05
F4	451±0.12	3.21±0.29	5.18±0.04	0.50±0.06
F5	454±0.08	3.18±0.40	5.30±0.05	0.50±0.10
F6	452±0.20	3.28±0.28	5.32±0.04	0.48±0.05
F7	449±0.08	3.18±0.30	5.60±0.04	0.48±0.12
F8	453±0.07	3.4±0.28	5.65±0.05	0.42±0.08
F9	451±0.06	3.32±0.28	5.58±0.04	0.45±0.08

* The results represent the average of the three notes ± SD

Wetting time:
The values, which show that all superdisintegrants have excellent hydrophilicity, were found to be between 29 and 41.6 sec.

Modified disintegration test:
The modified disintegration times for the various formulations, with values ranging from 34 to 43.6 seconds. F3, which contains 5% SSG, has the lowest disintegration time of all the formulations.

Water absorption ratio:
The values are between 25.31 to 29.2 in range. In comparison to formulations with higher concentrations of superdisintegrants, formulations with lesser concentrations exhibit lower water absorption ratios, which may be due to reduced swelling property.

***In Vitro* dispersion time:**
The results fall between 62 and 77 seconds. The findings indicated that crospovidone is the greatest super disintegrant, which may be due to its ability to produce porous tablets quickly and with little swelling efficacy, high water uptake capacity, and spongy nature. Additionally, the results demonstrated that the In Vitro dispersion time decreases as superdisintegrant concentration rises.

Table 6: Rapidly disintegrating properties

Formulation	Wetting period* (sec)	In Vitro Disintegration period* (sec)	Water absorption ratio*	In Vitro dispersion time* (sec)	% Medicine content*
F1	37.0±1.0	39.0±0.2	26.28±1.48	72.8±0.53	99.48±0.48
F2	35.2±1.6	41.1±0.5	25.38±1.12	69.8±0.38	99.68±0.58
F3	30.0±1.8	35.2±0.4	28.8±1.38	63.0±0.58	99.78±0.62
F4	33.9±1.3	42.8±0.6	27.02±1.08	76.0±0.68	99.08±0.48
F5	39.8±1.1	41.8±0.2	25.92±1.28	66.4±0.38	99.38±0.58
F6	32.8±1.5	36.5±0.2	28.08±1.48	65.1±0.68	99.55±0.72
F7	42.2±1.4	48.8±0.3	27.04±1.58	75.2±0.76	99.15±0.35
F8	36.0±1.4	38.8±0.4	26.90±1.72	71.8±0.62	99.35±0.62
F9	34.1±1.2	37.9±0.2	28.98±1.12	66.9±0.58	99.18±0.58

*Outcomes are the mean of 3 observations ± SD

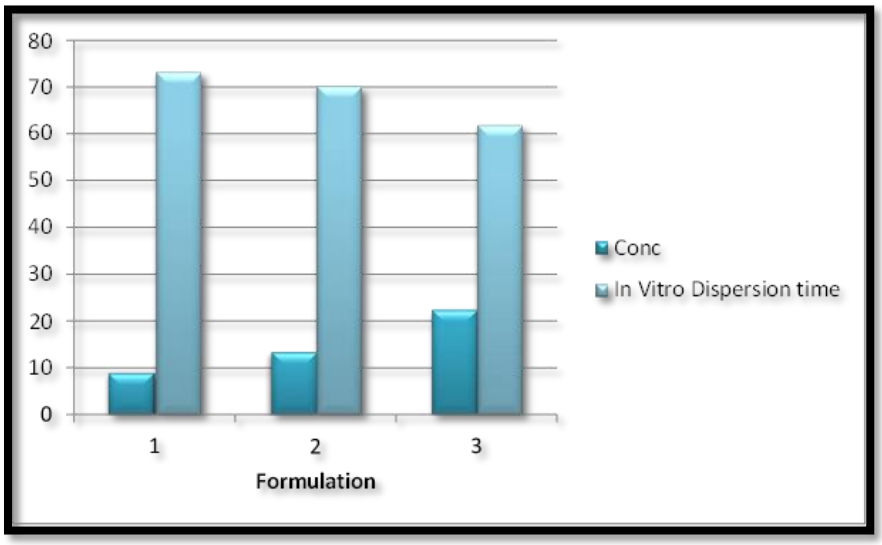

Fig 1. Relative diagram of conc. Vs In Vitro Dispersion time of F1, F2,F3

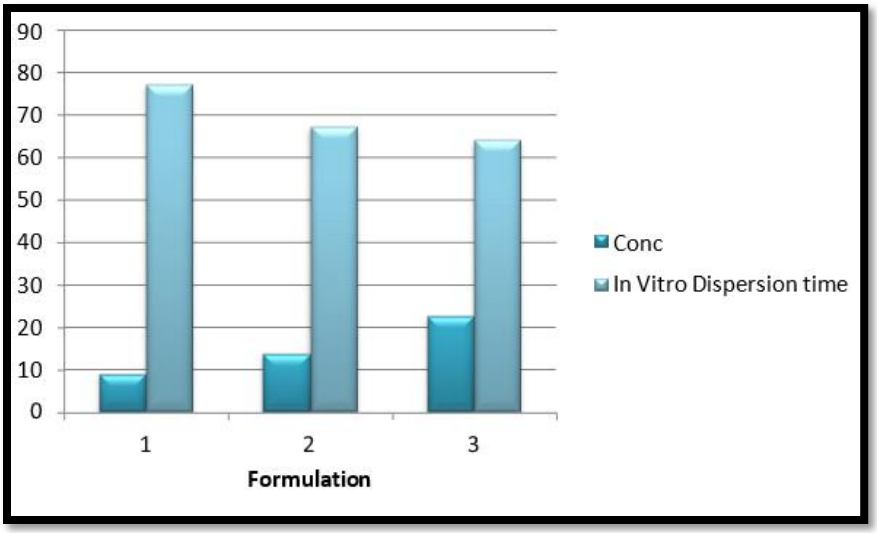

Fig 2. Comparative display of Concentration and In Vitro Dispersion time of F4, F5,F6

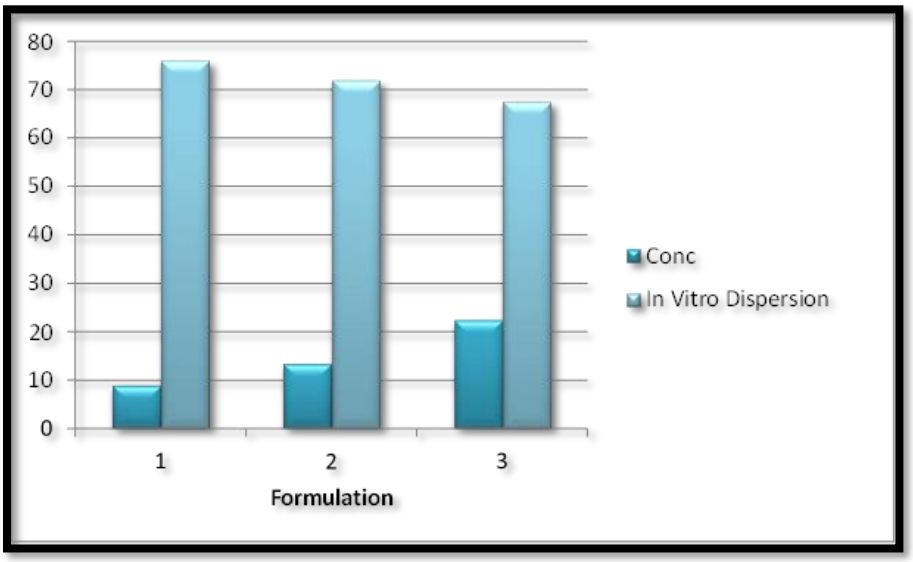

Fig 3. Comparative graph of Concentration and In Vitro Dispersion time of F7, F8, F9

***In Vitro* drug release:**

At the end of 15 minutes, the medication release for formulations F1 to F9 is, respectively, 94.7%, 95.6%, 99.5%, 91.9%, 94.2%, 96.4%, 90.0%, 92.6%, and 94.8% of aprepitant. All of the formulations' rapid dissolution may be caused by the tablets' speedy breakdown into tiny particles and quick absorption. As a result, formulation F3, which comprises 5% of CP in comparison to other preparations comprising SSG and CCS, demonstrated the greatest drug release, or 98.5%, at the end of 15 minutes. It might be caused by sodium starch glycolate, which has a higher tendency to swell, and croscarmellose sodium, which has a lower water absorption rate.

Table 7: In Vitro drug release outline of all preparations

Formulation	In Vitro % medication release				
	3	6	9	12	15
F1	63.8±0.88	72.0±0.76	79.8±0.88	86.9±1.12	93.9±0.86
F2	65.9±1.08	71.9±1.12	78.9±0.76	85.8±0.88	94.9±0.68
F3	70.0±0.88	71.9±1.08	77.9±0.90	89.0±1.02	98.9±1.08
F4	67.8±0.90	70.9±0.88	77.8±0.86	86.0±1.08	92.1±0.82
F5	68.9±1.12	74.0±1.06	78.8±0.88	86.8.0±0.1	93.9±0.76
F6	67.8±1.08	72.8±0.84	75.8±0.76	87.9±1.12	95.9±1.04
F7	64.9±0.84	70.6±0.78	75.8±1.12	83.9±1.08	91.0±0.88
F8	66.9±0.76	71.8±0.86	78.9±0.92	85.9±1.02	91.9±0.78
F9	67.8±1.12	73.8±1.14	78.9±0.88	87.8±1.14	93.7±0.88

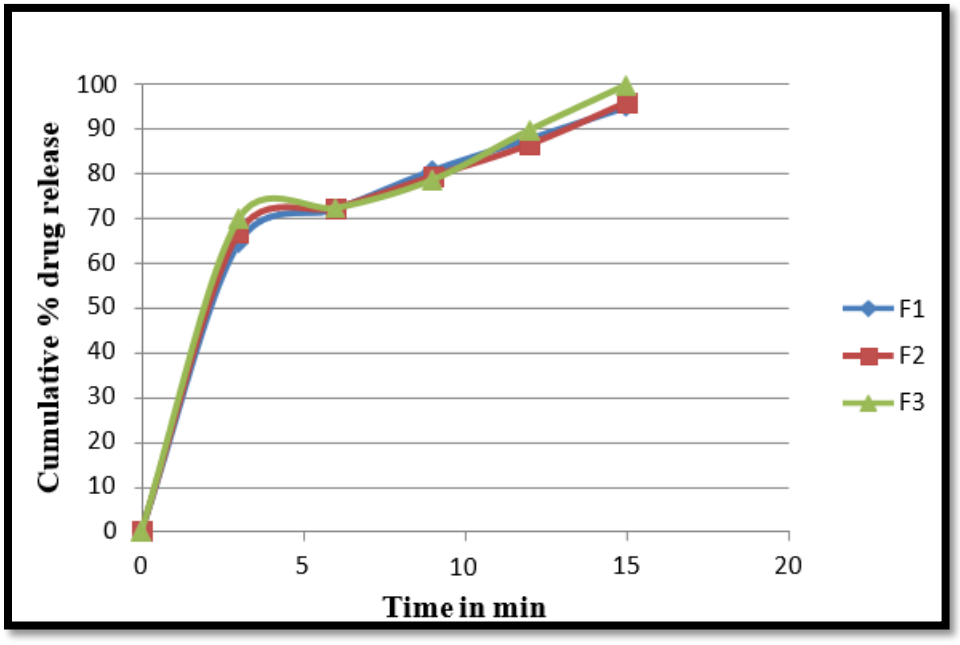

Fig 4. Comparative dissolution outline of F1, F2, F3

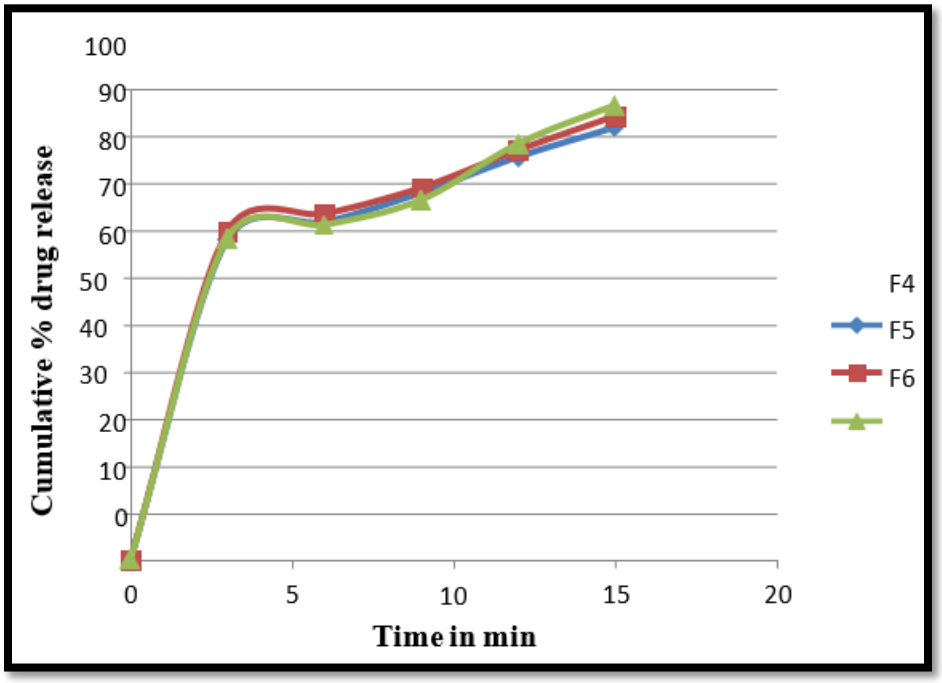

Fig 5. Comparative dissolution profile of F4, F5, F6

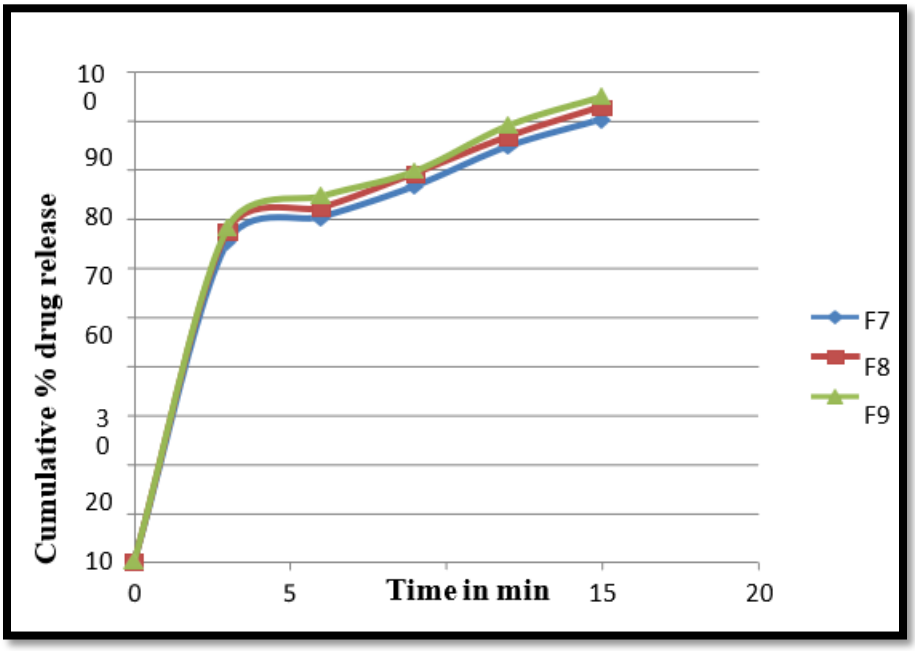

Fig 6. Comparative dissolution profile of F7, F8, F9

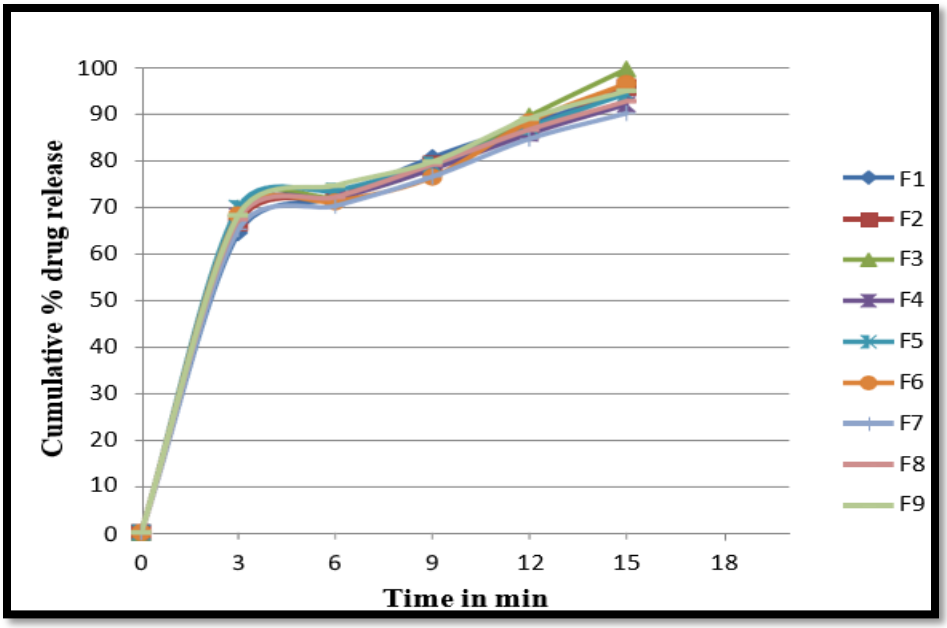

Fig 7. Dissolution profile of all formulations

Drug content:
The proportion medication content of many preparations is between 99.16 and 99.88%.
Stability study:
In a stability chamber, the formulation F3 was maintained for a month at 40°C and 75°RH as part of an accelerated stability investigation. No changes in color or flavor were noticed, and the tablets had no discernible unpleasant aroma.

Table 8: Stability trial of the Aprepitant ODT

S.No	Parameters	Units	F3			
			15 Days	30 Days	45 Days	60 Days
1.	Taste	As per conditions	Not bitter			
2.	Hardness	Kg / cm^2	3.30±0.41	3.28±0.35	3.25±0.45	3.24±0.28
3.	Friability	% w/w	0.43±0.26	0.44±0.30	0.42±0.38	0.41±0.28
4.	Disintegration time	Sec	34.9±0.3	35.0±0.3	33.9±0.4	32.8±0.4
5.	Wetting time	Sec	27.8.0±1.6	28.0±0.2	27.0±0.2	25.9±0.8
6.	Assay	%	99.90±0.4	99.60±0.6	99.15±0.25	98.6±0.3

CONCLUSION:

ODTs were develop to prevent the choking issues that frequently arise with tablet dosage forms. The ODTs dissolve in the mouth in a fraction of seconds deprived of need for the water, releasing the greatest amount of medicine within a short period of time and having an instant impact. The goal of the current work is to articulate and assess orodispersible tablets of taste-masked aprepitant in order to increase its current bioavailability of 70%. Since the Aprepitant has a harsh taste, it has been necessary to mask it using the polymer Eudragit E100, a cationic copolymer made by mass extrusion of dimethylaminomethyl methacrylate, butyl methacrylate, and methyl methacrylate. The physical properties, disintegration, In Vitro dissolution, and stability study of each prepared ODT formulation were all assessed. The formulations' hardness (F1-F9) ranged from 3.13 to 3.4 Kg/cm2, suggesting strong mechanical strength, and their thickness ranged from 5.13 to 5.72 mm. Friability and weight fluctuation were discovered to be within permitted ranges. All formulations' in vitro dispersion times were measured, and it was found that the in vitro dispersion times get shorter as superdisintegrant concentration gets higher. All of the formulations underwent a 15-minute in vitro dissolving trial, and the formulation with the highest results—F3—showed 99.5% medication release at the end of the test. The chosen formulation was put through a 60-day short-term stability trial, and results showed no discernible change.

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