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Design development and Evaluation of taste masked oral disintegrating tablets of atenolol- An approach to improve disintegration and onset of action

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ABSTRACT

Atenolol is β1-selective adrenergic blocking agent and widely used in the treatment of hypertension and angina pectoris. Administration of conventional tablets of atenolol has been reported to exhibit fluctuation in the plasma drug levels, resulting either in manifestation of side effects or reduction in drug concentration at the receptor site. The objective of this research was to mask the metallic taste of Atenolol and to formulate an orally disintegrating tablet (ODT). Taste masking was done by complexing Atenolol with Eudragit EPO in different ratios by solvent evaporation method. Drug-polymer complex were evaluated for drug content, in-vivo taste evaluation and molecular property. 1:2 ratio of drug-polymer complex did not show drug release in SSF and was considered as taste masked. Drug-polymer complex was then formulated into orally disintegrating tablets by direct compression by using different concentrations of superdisintegrants. Tablets were evaluated for weight variation, hardness, thickness, friability, drug content, wetting time, water absorption ratio, *in vitro* disintegration time and cumulative percentage drug release. Tablets of F6 formulation containing 6% crospovidone showed faster disintegration within 22.6 seconds. Taste evaluation studies conducted on eight healthy human volunteers.

Keywords: atenolol, onset of action

INTRODUCTION

Among the available pharmaceutical dosage forms, tablets are the most widely used dosage form because of their convenience in terms of self-medication, ease of administration, accurate dosage, compactness, good stability and ease of manufacturing. The Elderly constitute a major portion of world population today. These people will experience deterioration of their physiological and physical abilities like dysphagia (difficulty in swallowing). Pediatric patients may suffer from ingestion problems of their underdeveloped muscular and nervous system (Shery et al., 2009). In order to overcome this problem, a new drug delivery system has been developed known as Orally Disintegrating Tablets (ODTs). Orally Disintegrating Tablets are solid dosage form containing medicinal substances which disintegrates/dissolves rapidly upon contact with saliva. When these tablets are placed in oral cavity, saliva penetrates into the pores causing rapid disintegration. These tablets are beneficial for the patients suffering from nausea and vomiting, those with mental disorders, bedridden and those who do not have easy access of water. Atenolol [4-[2-hydroxy-3-isopropyl-aminopropoxy]-phenyl-acetamide] belongs to the category of β-blockers and, more specifically, it is a hydrophilic β1-receptor blocking agent. This drug is of therapeutic value in the treatment of various cardiovascular disorders, such as angina pectoris, cardiac arrhythmia and hypertention [1]. β-blockers are exceptionally toxic and most of them have a narrow therapeutic range [2]. Gas chromatography (GC) with mass spectrometry or electron capture detector has been used extensively for the determination of atenolol [2,3]. High performance liquid chromatography (HPLC) has also been extensively used for the determination of atenolol [4,5]. Immunoassays have also been used for the determination of this β-adrenoreceptor blocking agent [6]. Atenolol, 4-[2-hydroxy-3-[(1-methylethyl) amino] propoxy] benzene acetamide is a relatively polar hydrophilic compound with a log partition coefficient (octanol/ water) of 0.23. Lipid insoluble hydrophilic compounds such as atenolol, sotalol, nadolol are excreted only by the kidneys and have low brain penetration. Atenolol is a selective Bi-adrenoceptor antagonist, applied in the treatment of numerous cardiovascular disorders

including: hypertension, angina, acute myocardial infarction, supraventricular tachycardia, ventricular tachycardia, and the symptoms of alcohol withdrawal *via* restricting certain nerve impulses, thereby controlling the rate and force of contraction and consequently reducing blood pressure in addition to its treatment of Angina Pectoris. Atenolol is marketed as tablets and an injectable formulation [7,8]. Atenolol has a *pKa* of 9.6; it undergoes ionization in the stomach and intestine thus its oral bioavailability is low due to inefficient absorption through membranes. The bioavailability of atenolol is between 45% and 55% of the given dose and is not increased by administration of the drug in a solution form [9]. About 50% of administered atenolol is absorbed; however, most of the absorbed quantity reaches the systemic circulation. Atenolol peak blood levels are reached within two to four hours after ingestion. Differently from propranolol or metoprolol, atenolol is resistant to metabolism by the liver and the absorbed dose is eliminated by renal excretion. More than 85% of I.V. dose is excreted in urine within 24 hours compared to 50% for an oral dose. Only 6-16% is protein-bound resulting in relatively consistent plasma drug levels with about a four-fold inter-patient variation. The elimination half-life of atenolol is between 6 to 7 hours and there is no alteration of kinetic profile of a drug by chronic administration. Atenolol is one of the most important medicines used for prevention of several types of arrhythmias in childhood, but unfortunately it is still unlicensed [10]. On the other hand, atenolol is indicated as a first-step therapy for hypertension in elderly patients, who have difficulty in swallowing and, thus, tablets and capsules are frequently avoided. The ease of administration makes a liquid formulation an ideal dosage form for such patients [11]. Therefore, extemporaneous compounding (off label), involves preparation of an oral liquid from a pure drug powder is required. However, formulations compounded from tablets and pure active drug suffer instability and are only stable for less than one week [12, 13, 14]. Furthermore, atenolol bitterness is considered as a great challenge to health sector when used among children and geriatrics [15]. The main problem in oral administration of bitter drugs such as atenolol is incompliance by the patients [16] and this can be overcome by masking the bitterness of the drug either by decreasing its oral solubility on ingestion or eliminating the interaction of drug particles to taste buds [17].

METHODOLOGY

Preparation of standard graph of Atenolol in 0.1N HCl

Accurately weighed amount (100 mg) of the drug was dissolved in 0.1N HCl in 100 ml volumetric flask and make up the volume to 100 ml with 0.1N HCl. From this stock solution (1mg/ml) 10 ml of solution is with drawn into a 100 ml volumetric flask and the volume was made up with 0.1N HCl. From this second solution (100µg/ml) different concentration 5, 10, 15, 20, 25, 30, 35, 40, 45µg/ml is prepared and their corresponding absorbance was measured at 225 nm in a UV/Visible spectrophotometer.

Preparation of standard graph of Atenolol in pH 6.8 Phoshpate buffer

Accurately weighed amount (100 mg) of the drug was dissolved was dissolved in 50 ml solvent mixture of phosphate buffer (pH 6.8) and methanol in the ratio of 1:1, which constitutes the stock solution of 1 mg/ml. Form this stock solution (1mg/ml) 10 ml of solution is with drawn into a 100 ml volumetric flask and the volume was made up with pH 6.8 phosphate buffer. From this second solution (100µg/ml) different concentration 5, 10, 15, 20, 25, 30, 35µg/ml are prepared and their corresponding absorbance was measured at 225 nm in a UV/Visible spectrophotometer.

Fourier transform infrared spectroscopy (FTIR)

FTIR studies were performed on drug, polymer, drug-polymer complex. Physical mixture and the optimized formulation using Bruker FTIR. The samples were analyzed between wave numbers 4000 and 400 cm^{-1}.

Preparation of Drug Polymer Complex

Atenolol and Eudragit EPO complex was prepared by solvent evaporation method. Saturated stock solutions of Atenolol and Eudragit EPO were prepared in absolute Ethanol. Aliquots of drug and polymer solutions were taken to obtain various ratios (1:1, 1:2 and 1:3) and mixed continuously at 150rpm on a magnetic stirrer. Stirring was allowed to continue until the solvent is completely evaporated (Shagufta et al., 2007). After this mixture was kept at 35ºC for 2 hours and dried at room temperature for 24 hours to obtain a hard matrix. Then the hard matrix is subsequently pulverized and screened through 60mesh to obtain the uniform sized fine powder of drug polymer complex (DPC) and it was finally stored in a tightly closed container for further studies.

Preparation of Atenolol ODTs by direct compression technique

Atenolol ODTs were prepared using direct compression technique. Direct compression technique is a convenient method. Different formulations of Atenolol ODTs were designed to be prepared by direct compression technique using four super disintegrants, (Croscarmellose sodium, Crosspovidone, Sodium starch glycolate and Low-substituted hydroxypropyl cellulose). Superdisintegrants is varied with 3 different concentrations (i.e., 2, 4, 6% respectively) keeping all other ingredients constant, there are assigned with formulation codes shown in Table 1.

Table 1: Formulation codes

Disintegrant used	Concentration (%)	Formulation code
Croscarmellose sodium	2	F1
	4	F2
	6	F3
Crospovidone	2	F4
	4	F5
	6	F6
Sodium starch glycolate	2	F7

	4 6	F8 F9
Low-substituted hydroxyl propyl cellulose	2 4 6	F10 F11 F12

Procedure

Drug-Polymer Complex, superdisintegrants, microcrystalline cellulose, sodiumsaccharin, orange flavor were accurately weighed and passed through a 40-mesh screen to get uniform size particles and mixed in a glass mortar for 15 minutes. The obtained blend was lubricated with sodium stearyl fumarate and talc and mixing was continued for further 5 minutes. The resultant mixture was directly compressed into tablets by using 8mm round concave faced punch of Rotary tabletting machine. Compression force was kept constant for all formulations. Table 5.2 outlines the compositions of various ODT formulations.

Table 2: Quantitative Composition of Atenolol Orally Disintegrating Tablets

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Drug-polymer complex(1:2)	75	75	75	75	75	75	75	75	75	75	75	75
Croscarmellose sodium	3	6	9	-	-	-	-	-	-	-	-	-
Crospovidone	-	-	-	3	6	9	-	-	-	-	-	-
Sodium starch glycolate	-	-	-	-	-	-	3	6	9	-	-	-
L-HPC	-	-	-	-	-	-	-	-	-	3	6	9
Sodium stearyl fumarate(1%)	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Talc (2%)	3	3	3	3	3	3	3	3	3	3	3	3
Orange flavor	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	05	0.5	0.5	0.5
Sodium saccharin(2%)	3	3	3	3	3	3	3	3	3	3	3	3
Microcrystalline cellulose	41	38	35	41	38	35	41	38	35	41	38	35
Pearlitol SD200	20	20	20	20	20	20	20	20	20	20	20	20

Total weight of tablets is 150 mg.

Evaluation of Drug content in Drug Polymer Complex (DPC) and In-Vitro Taste Evaluation

Drug content was determined by dissolving 100mg of DPC in100ml of simulated gastric fluid (SGF) and analyzing diluted sample at 225nm by UV-spectrophotometer. In-Vitro taste was evaluated by determining drug release in simulated salivary fluid (SSF) (pH 6.8) to predict drug release in human saliva. DPC, equivalent to 25mg of Atenolol i.e., its dose, was placed in 10ml of SSF and shaken for 60 seconds. The amount of drug released was analyzed at 225nm by UV-spectrophotometer.

Pre formulation Studies

It is the first step in rational development of dosage forms of drug substance. Pre formulation testing is defined as investigation of physical and chemical properties of a drug substance alone and when combined with excipients. It gives information needed to define the nature of the drug substance and provide frame work for the drug combination with pharmaceutical excipients in the dosage form.

Bulk Density (Db)

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weight powder (passed through standard sieve # 20) into a measuring cylinder and initial weight was noted. This initial volume is called the bulk volume. From this the bulk density is calculated according to the formula mentioned below. It is expressed in g/ml and is given by

Db = M/ Vb

Where,

M is the mass of powder

Vb is the bulk volume of the powder.

Tapped Density (Dt)

It is the ratio of total mass of the powder to the tapped volume of the powder. Volume was measured by tapping the powder for 750 times and the tapped volume was noted if the difference between these two volumes is less than 2%. If it is more than 2%, tapping is continued for 1250 times and tapped volume was noted. Tapping was continued until the difference between successive volumes is less than 2 % (in a bulk density apparatus). It is expressed in g/ml and is given by

$D_t = M / V_t$
Where,
M is the mass of powder
V_t is the tapped volume of the powder.

Carr's index (or) % compressibility
It indicates powder flow properties. It is expressed in percentage and is give

$$I = \frac{\square\square - \square\square}{\square\square} \times \square\square\square$$

Where,
D_t is the tapped density of the powder and
Db is the bulk density of the powder.

Table 5.3: Relationship between % compressibility and flowability

% Compressibility	Flowability
5 – 12	Excellent
12 – 16	Good
18 – 21	Fair passable
23 – 35	Poor
33 – 38	Very poor
> 40	Very very poor

Hausner ratio

Hausner ratio is an indirect index of ease of powder flow. It is calculated by the following formula.

$$\textbf{Hausner ratio} = \frac{\square\square}{\square\square}$$

Where,
Dt is the tapped density.
Db is the bulk density.
Lower hausner ratio (<1.25) indicates better flow properties than higher ones (>1.25).

Angle of Repose

The friction forces in a loose powder can be measured by the angle of repose. It is an indicative of the flow properties of the powder. It is defined as maximum angle possible between the surface of the pile of powder and the horizontal plane.

$\tan(\theta) = h / r$
$\theta = \tan^{-1}(h / r)$
Where,
θ is the angle of repose.
h is the height in cms
r is the radius in cms.

The powder mixture was allowed to flow through the funnel fixed to a stand at definite height (h). The angle of repose was then calculated by measuring the height and radius of the heap of powder formed. Care was taken to see that the powder particles slip and roll over each other through the sides of the funnel. Relationship between angle of repose and powder flow property.

Table 3: Angle of Repose as an Indication of Powder Flow Properties

Angle of repose	Flow
<25	Excellent
25 – 30	Good
30 – 40	Passable
>40	Very poor

Evaluation of orally disintegration tablet formulations

Different quality control tests were performed for all the ODT formulations to check whether these have met the specifications given in USP along with other *Invitro* tests like wetting time and water absorption ratio.

Various Invitro tests performed are

- Weight variation test
- Thickness measurement
- Hardness and Friability
- Content uniformity
- Wetting time and Water absorption ratio
- Disintegration Time
- Dissolution test

Weight variation test

Twenty tablets were randomly selected from each formulation and their average weight was calculated using digital balance. Individual weight of each tablet was also calculated using the same and compared with the average

weight. The Mean ± S.D. were noted. The tablets meet USP specifications if not more than two tablets outside the percentage limit and if no tablet differs by more than two times the percentage limit.

Table 4: Weight Variation Limits

IP/BP	Limit	USP
80 mg or less	10%	130mg or less
More than 80mg or Less than 250mg	7.5%	130mg to 324mg
250mg or more	5%	More than 324mg

Thickness

Randomly ten tablets were taken from each formulation and their thickness was measured using a digital screw gauge. The individual tablet was placed between two anvils of the screwguage and sliding knob was rotated until the tablet was tightly fitted. The digital reading displayed was noted. The Mean ± S.D. were noted. The tablet thickness should be controlled within a ± 5% variation of standard value.

Hardness

The tablet hardness of different formulations was measured using the Monsanto hardness tester. The tester consists of a barrel containing a compressible spring held between two plungers. The lower plunger was placed in contact with the tablet, and a zero was taken. The upper plunger was then forced against the spring by turning a threaded bolt until the tablet fractures. As the spring is compressed, a pointer rides along a gauge in the barrel to indicate the force. The force of fracture is recorded, and the zero force reading is deducted from it. Generally, a minimum hardness of 4 kg is considered acceptable for uncoated tablets. The hardness for ODTs should be preferably 1-3 kg.

Friability

This test is performed using a laboratory friability tester known as Roche Friabilator. Ten tablets were weighed and placed in a plastic chambered friabilator attached to a motor, which revolves at a speed of 25 rpm, dropping the tablets from a distance of 6 inches with each revolution. The tablets were subjected to 100 revolutions for 4 minutes. After the process, these tablets were dedusted and reweighed. Percentage loss of tablet weight was calculated.

$$\% \text{ Friability} = (W_1 - W_2) \times 100/W_1$$

Where,

W_1 = Initial weight of the 10 tablets.

W_2 = Final weight of the 10 tablets.

Friability values below 1% are generally acceptable.

Content uniformity

Ten tablets were randomly selected, weighed and finely powdered and quantity of powder equivalent to one tablet was added to 100 ml 0.1N HCl in a conical flask. Conical flasks were placed on a rotary shaker. An aliquot of solution was centrifuged and supernatant was filtered through a 0.22µ filter. Absorbance of the resulted supernatant solution was measured using U.V Visible spectrophotometer at a wavelength of 225nm against 0.1N HCl as blank. Concentrations were calculated with the help of standard graph and total amount present in the formulation was calculated.

Wetting time

A piece of tissue paper folded twice was placed in a small petri dish containing 6 ml of water. A water-soluble dye phenolphthalein was added to the petri dish. The dye solution is used to identify the complete wetting of the tablet surface (Abdelbary et al, 2009). A tablet was carefully placed on the surface of tissue paper in the petri dish at room temperature. The time required for water to reach the upper surface of the tablets and completely wet them was noted as the wetting time. To check for reproducibility, the measurements were carried out in replicates (n=6). The wetting time was recorded using a stopwatch.

Water absorption ratio (R)

The weight of the tablet before keeping in the petri dish was noted (W_b) using Shimadzu digital balance. The wetted tablet from the petri dish was taken and reweighed (W_a) using the same. The Water absorption ratio, R, was determined according to the following equation:

$$R = 100 (Wa - W_b) / W_b$$

Where W_b and W_a are the weight before and after water absorption respectively.

Disintegration time

Disintegration time is considered to be one of the important criteria in selecting the best formulation. To achieve correlation between disintegration time *In vitro* and *In vivo* (in oral cavity) several methods were proposed, developed and followed at their convenience. One of the simple method followed is described below.

Method: Disintegration time was also measured using a modified disintegration method (n=6). For this purpose, a petri dish (10 cm diameter) was filled with 10 ml of water. The tablet was carefully put in the center of the petri dish and the time for the tablet to completely disintegrate into fine particles was noted using a stop watch.

Dissolution test

Method: Dissolution test was carried out using USP rotating paddle method (apparatus 2). The stirring rate was 50 rpm 0.1N HCl was used as dissolution medium (900 ml) and was maintained at 37 ± 1^0C. Samples of 5ml were withdrawn at predetermined intervals (5, 10, 15, 20, 30, 40, 50 and 60 min), filtered and replaced with 5ml of fresh dissolution medium. The collected samples were suitably diluted with dissolution fluid, where ever necessary and were analyzed for the Atenolol at 225 nm by using UV spectrophotometer. Each dissolution study was performed for three times and mean values were taken.

In Vivo taste evaluation

Taste evaluation was conducted on eight healthy male human volunteers from whom informed consent was obtained. The Drug-Polymer complex equivalent of 25 mg of Atenolol was place on the tongue for 30 seconds and then spat out. Optimized ODT formulation (containing 25 mg of Atenolol) was placed on the tongue until complete disintegration (Jianchen et al., 2008). Taste was evaluated and assigned according to bitterness intensity scale, i.e. 0=tasteless, 1=slight bitter, 2=moderate bitter, 3=strong bitter.

RESULTS AND DISCUSSION

Construction of calibration curve of Atenolol in 0.1N HCl

The calibration curve of Atenolol has shown good linearity with R^2 value 0.994 in 0.1N HCl by plotting concentration on X-axis and absorbance on Y-axis.

Table 5: Calibration curve data of Atenolol in 0.1N HCl

Concentration (µg/ml)	Absorbance (nm)
0	0
5	0.089
10	0.153
15	0.257
20	0.318
25	0.39
30	0.438
35	0.522
40	0.583
45	0.628

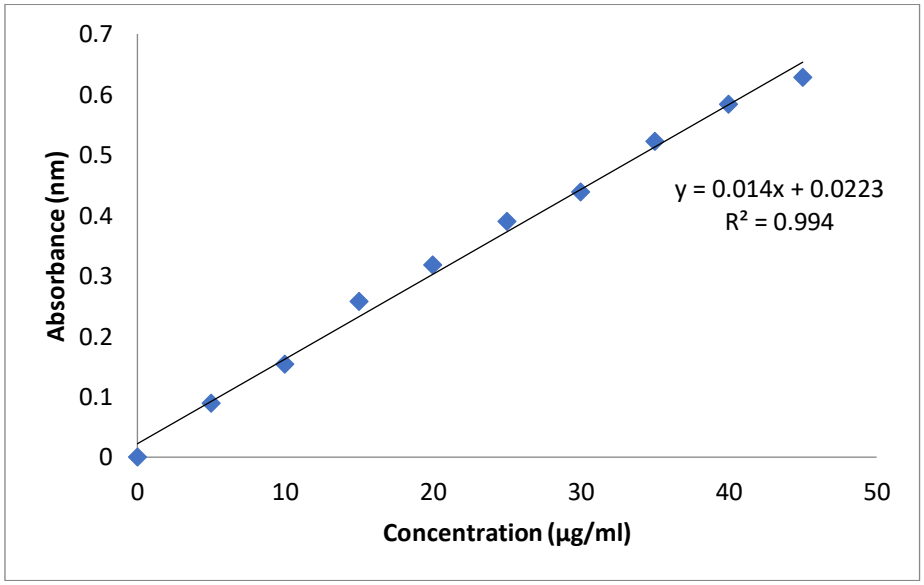

Fig 1: Calibration curve of Atenolol in 0.1N HCl

Construction of calibration curve of Atenolol in pH 6.8 Phosphate buffer

The calibration curve of Atenolol has shown good linearity with R^2 value 0.994 in pH 6.8 Phosphate buffer by plotting concentration on X-axis and absorbance on Y-axis.

Table 6: Calibration curve data of Atenolol in pH 6.8 Phosphate buffer.

Concentration (µg/ml)	Absorbance (nm)
0	0
5	0.086

10	0.176
15	0.289
20	0.398
25	0.476
30	0.558
35	0.614

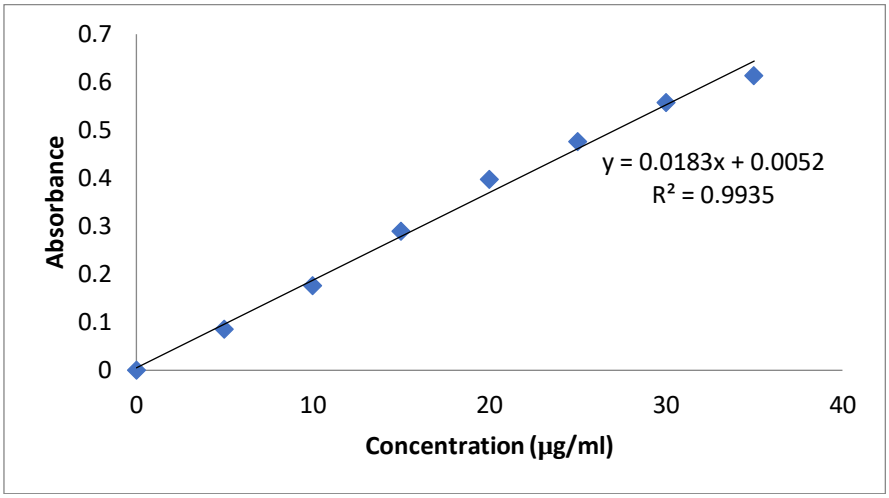

Fig 2: Calibration curve data of Atenolol in pH 6.8 Phosphate buffer.

Fourier Transform Infrared Spectroscopy (FTIR)

FTIR analysis derivative showed a characteristic peak at 3084.18 cm^{-1} this is due to C-H aromatic stretching was used to study the possible chemical interaction between the drug and polymer. The pure drug which is a atenolol. The peak at 3345.61 cm^{-1} is due to N-H stretch in the amide.The peak at 2962 cm^{-1} indicative of C-H stretch in the alkane. Eudragit EPO which is an methacrylic acid ester showed important peaks at 1723.38 cm^{-1} indicative of C=O stretch of the ester group. The peaks at 2928.88 cm^{-1} indicative of C-H stretch in the alkane and 2767.71 cm^{-1} can be assigned to the dimethyl amino group.

The FTIR spectra of Drug Polymer Complex (DPC) displayed all the characteristic peaks of both drug and polymer. The C=O stretch and C-H stretch in dimethyl amino group and C-H stretch in alkane of drug-polymer complex were detected in the same position of polymer, which indicates that the drug is completely entrapped in the polymer. Consequently the FTIR of drug-polymer physical mixture showed no signigiciant shift or reduction in intensity of peaks of atenolol. The physical mixture of tablet showed additional characteristic peak at 3344.78 cm^{-1} indicative of free O-H stretch. This peak may be due to presence of microcrystalline cellulose.

IR Spectra	Peak of Functional gruoups [Wave length (cm-1)]			
	N-H Stretching (amide)	C-O Stretching (ester)	C-N Stretching (amide)	C-H Stretching (alkane)
Atenolol	3345.61	1035.37	1238.11	2962.90
Atenolol + Eudragit EPO	3344	1036	1238	2952
Atenolol + CCS	3348	1070	1240	2958
Atenolol + CP	3346	1078	1241	2950
Atenolol + SSG	3339	1090	1238	2951
Atenolol + L-HPC	3348	1075	1242	2960

Table 7: FTIR Interpretation of Drug and Excipients

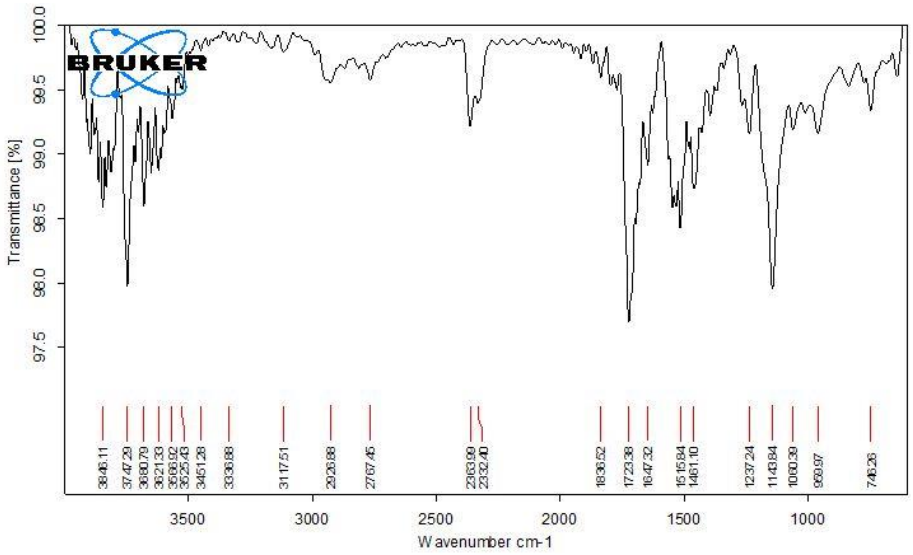

Figure 3: FTIR spectra of Atenolol

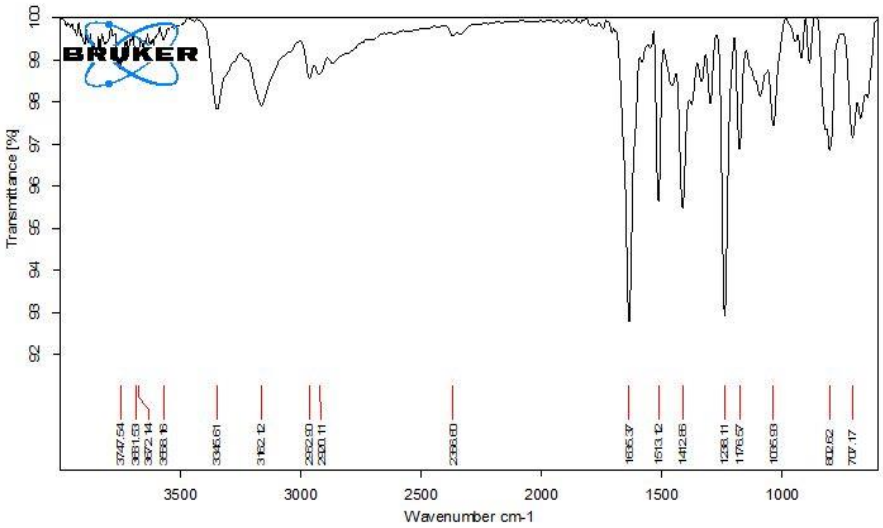

Figure 4: FTIR spectra of Eudragit EPO

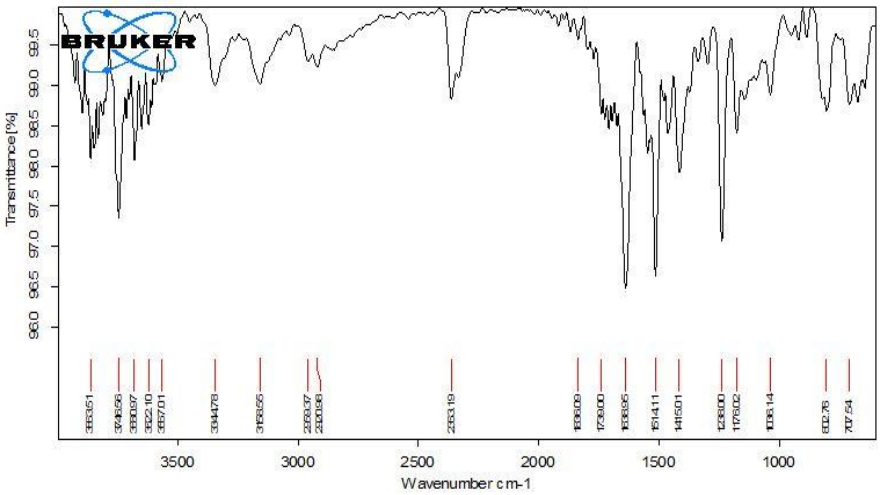

Figure 5: FTIR spectra of Atenolol+Eudragit EPO

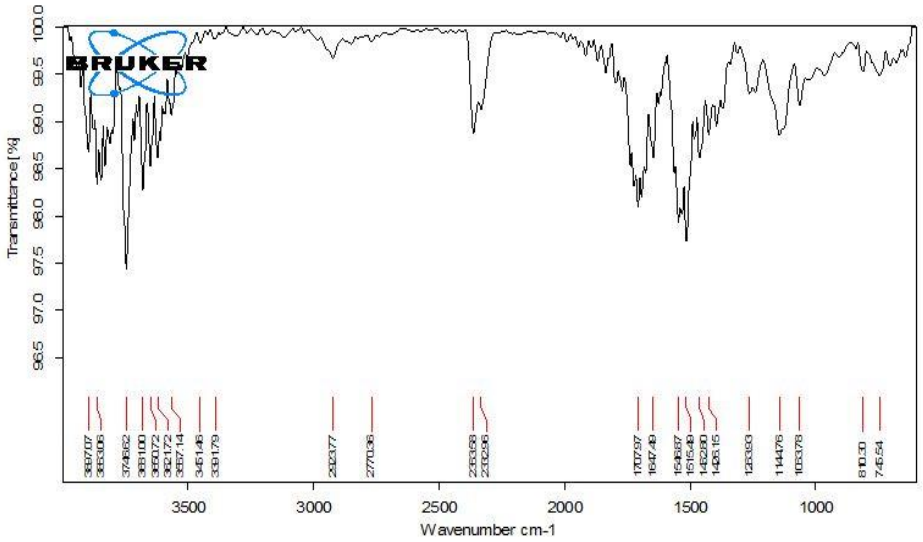

Figure 6: FTIR spectra of Tablet Total blend

Evaluation of Drug content in Drug-Polymer Complex (DPC) and InVitro Taste Evaluation

Percentage drug loading in DPC was found to be 98.05% for 1:2 ratio compared to 1:1 and 1:3 in which drug loading is 92% and 88.7%. No drug release was observed in SSF from complexes with drug-polymer ratio of 1:2 compared to 1:1 and 1:3 ratios, therefore, the ratio 1:2 was considered the optimal DPC with complete taste masking of metallic taste of Atenolol.

Table 8: Evaluation of Drug content and *InVitro* Taste Evaluation of DPC

S. No	Drug-Polymer ratio in DPC	Amount of Atenolol per 100 mg of DPC	%Drug Dissolved in SSF
1	1:1	48.71±0.22	9.25±1.09
2	1:2	31.42±0.15	0.4±0.16
3	1:3	24.76±0.5	4.12±0.52

Table 9: Micromeritic properties of Atenolol blends:

Formulation	Angle of repose (θ)	Bulk density (g/cc)	Tapped density(g/cc)	Compressibility index (%)	Hausner ratio
F1	26.65±0.329	0.4186±0.008	0.4866±0.011	13.97±0.282	1.16±0.003
F2	28.32±0.201	0.3750±0.006	0.4391±0.009	14.56±1.80	1.16±0.023
F3	25.36±0.098	0.3913±0.007	0.4615±0.010	15.20±1.62	1.17±0.023
F4	27.43±0.187	0.3833±0.014	0.4395±0.019	13.7±1.89	1.15±0.028
F5	28.50±0.067	0.4002±0.013	0.4669±0.017	14.28±1.77	1.16±0.025
F6	22.54±0.265	0.3997±0.009	0.4612±0.019	13.33±1.93	1.153±0.038
F7	26.65±0.055	0.4043±0.016	0.4751±0.016	14.8±1.87	1.166±0.026
F8	27.50±0.182	0.4073±0.011	0.4807±0.010	12.13±1.82	1.180±0.023
F9	27.54±0.137	0.4157±0.006	0.4923±0.016	15.15±1.93	1.184±0.033
F10	24.16±0.05	0.4000±0.011	0.4676±0.010	14.43±1.92	1.16±0.028
F11	23.15±0.07	0.3873±0.012	0.4505±0.019	13.98±1.91	1.16±0.026
F12	27.31±0.06	0.3790±0.006	0.4448±0.016	14.74±1.95	1.17±0.026

The formulated blends were evaluated and the results are shown in the table (6.2).The angle of repose was in the range of 22.54±0.265 to 28.50±0.067 indicating good flow property. The bulk density and tapped density was in the range of 0.3750±0.006 to 0.4186±0.008gm/cc and 0.4391±0.009 to 0.4923±0.016. The compressibility index and Hauser's ratio was in the range of 12.13±1.82 to 15.20±1.62% and 1.15±0.023 to 1.17±0.023 indicating good flow property.

Evaluation of Atenolol orally disintegrating tablets

The prepared tablets were evaluated for hardness, friability, thickness and weight variation (Table 6.3) for all the batches were found to be within the acceptable limits.

Table 10: Evaluation of Atenolol orally disintegrating tablets

Formulation	Weight variation*	Thickness**	Hardness***	% Friability**	Drug content***
F1	149.6±0.53	2.4±1.4	2.5±0.16	0.70	97.4±0.34
F2	150.2±0.43	2.4±0.05	2.5±0.18	0.57	101.1±0.7

F3	150.3±0.44	2.4±0.3	2.7±0.16	0.59	98.2±0.52
F4	149.6±0.65	2.5±0.08	2.5±0.16	0.76	99.5±0.84
F5	148.2±0.68	2.3±0.8	2.6±0.22	0.58	98.6±0.31
F6	149.5±0.14	2.5±0.07	2.5±0.23	0.36	99.7±0.52
F7	150.5±0.52	2.6±0.86	2.6±0.14	0.58	97.5±0.47
F8	150.3±0.42	2.6±0.2	2.8±0.13	0.83	99.7±0.65
F9	150.3±0.14	2.3±0.1	2.5±0.16	0.44	98.6±0.61
F10	149.6±0.21	2.5±0.21	2.4±0.12	0.74	97.8±0.56
F11	150.22±0.49	2.6±0.46	2.6±0.12	0.69	98.5±0.58
F12	150.3±0.38	2.5±0.21	2.4±0.21	0.55	99.3±0.36

*Results are the mean of 20 observations ± SD, **Results are the mean of 10 observations ± SD, ***Results are the mean of 3 observations ± SD

The values of weight variation for all the formulations were found to be in the range of 148.2±0.68 to 150.5±0.52. Thicknesses of all the formulations were found to be in the range of 2.3±0.11 to 2.6±0.86. The hardness was constantly maintained between 2.4±0.12 to 2.84±0.13 kg/cm^2 during compression. Friability for all the formulation shown less than 0.90% which is in the acceptable limits which indicates that the hardness was enough to withstand erosion on handling and storage.

Wetting time

Wetting time was determined for all the formulations. The wetting time for the optimized formulations is below one minute; this indicates quicker disintegration of the tablet. The values of wetting time lies between 42±0.6 to 162.6±1.18. Formulations with Crospovidone as disintegrant exhibited quicker Wetting time of tablets than compared to Sodium starch glycolate, Croscarmellose sodium and Low-substituted hydroxypropyl cellulose at equivalent concentrations (Figure 6.1). Faster wetting of tablets containing Crospovidone might be due to its rapid water absorbing nature involving both capillary and swelling mechanisms.

Water Absorption Ratio

Water Absorption Ratio, 'R' of formulations containing Crospovidone and Sodium starch glycolate were greater than that of Croscarmellose sodium and Low-substituted hydroxyl propyl cellulose. The values of Water Absorption Ratio for all the formulations were found to be in the range of 97.3±1.12 to 352.8±0.4. Water absorption ratio 'R' increased with an increase in superdisintegrants concentrations from 3-9%. The increase in 'R' might be due to increase in uptake of water for Crospovidone at higher concentrations (Figure 6.2).

In Vitro Disintegration Time

Disintegration time is considered to be important criteria in selecting the best ODT formulation. The *in vitro* disintegration time for all the formulations varied from 22.6 ± 0.52 to 142.6 ± 1.53 seconds. The rapid disintegration was seen in the formulations containing Crospovidone and Sodium starch glycolate. It might be due to its rapid water absorbing nature involving both capillary and swelling mechanisms, building up the pressure internally leading to the faster disintegration. It is also noticed that as the disintegrant concentration was increased from 3 to 9 % the time taken for disintegration was reduced. The disintegration time of formulation (F6) containing 6% CP was found to be lower (22.6 ± 0.82) and was selected as the best ODT formulation among all the 12 formulations.

Table 11: Evaluation of Atenolol orally disintegrating tablets

Formulation	Wetting time (sec)	Water absorption ratio (%)	In-Vitro Disintegration time (sec)
F1	112.6±1.06	132.8± 1.14	89.8±1.14
F2	91±0.89	172.6± 0.92	79±1.21
F3	66.2±1.03	198.8± 1.02	52±1.46
F4	62.6±0.85	242.4± 0.43	51± 0.89
F5	54.8±0.78	306.8± 1.12	42.6± 1.16
F6	42±0.6	352.8± 0.4	22.6± 0.82
F7	102.6±1.21	176.06± 1.06	82.3± 1.22
F8	86.6±1.14	212.3± 1.02	63.8±1.14
F9	63.8±0.65	253.1± 1.12	50.1± 1.46
F10	162.6±1.18	97.3± 1.12	142.6± 1.53
F11	128.5±1.03	112±0.7	110.5±1.27
F12	106.1±1.14	149.5±0.81	94.1±1.12

a: Mean±S.D., n=6 tablets, b: Mean±S.D., n=10, c: Mean±S.D., n=20

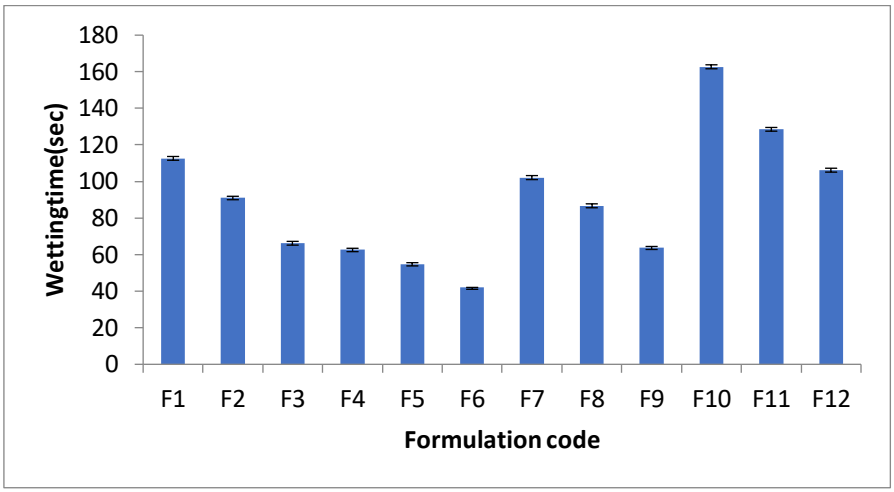

Fig 7: Graphical representation of wetting time of Atenolol ODTs prepared by varying concentrations of superdisintegrants.

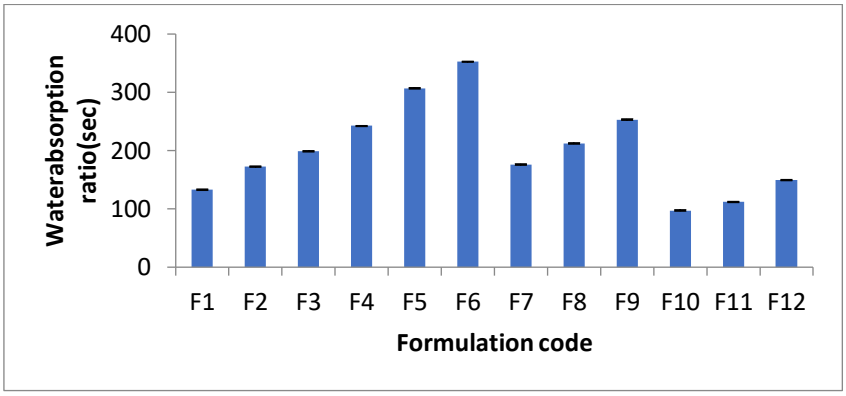

Fig 8: Graphical representation of water absorption ratio of Atenolol ODTs prepared by varying concentrations of superdisintegrants.

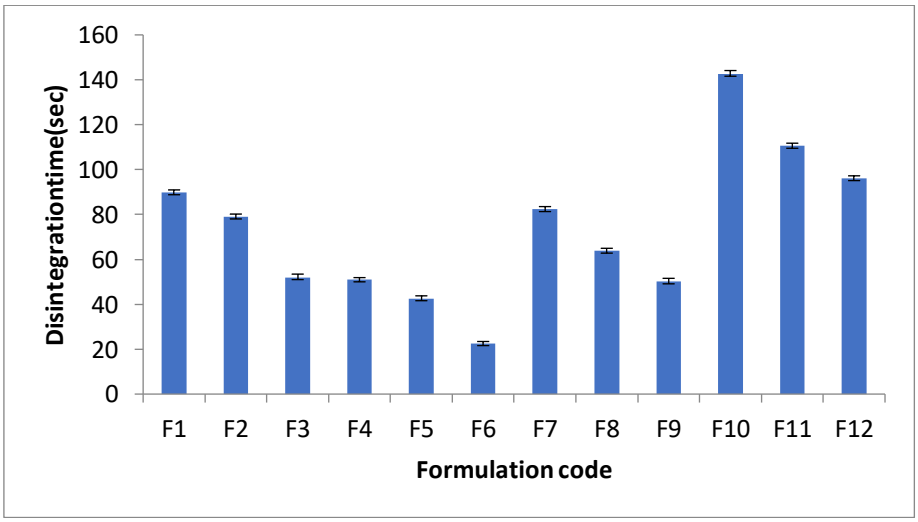

Fig 9: Graphical representation of disintegration time of Atenolol ODTs prepared by varying concentrations of superdisintegrants.

InVivo Taste evaluation

Taste evaluation was performed on Eight healthy human volunteers and the results were reported in the table 6.5. The bitterness of the drug was reduced or even masked after complexation with eudragit EPO in different ratios (1: 1, 1:2 and 1:3). In case of 1:1 ratio it was felt slightly bitter after 1 minute and it is apparent from the results that the increasing concentrations of the polymer have completely have completely masked the metallic taste of the drug. Since the drug is not in the native form and entrapped within the polymeric matrix, and there by reduction in the solubility of the drug in the saliva could have led to the masking of the metallic taste. Even though the Atenolol taste was masked with drug polymer complex (1:1, 1:2 and 1:3) ratios, we have

selected 1:2 for further studies, since higher amounts of polymer may retard the dissolution performance of the final fast disintegrating tablets of Atenolol.

Table 12: Comparative taste evaluation*

Degree of Bitterness					
Form of Atenolol	**10 seconds**	**30 seconds**	**1 minute**	**2minutes**	**5minutes**
DPC (1:1)	0	0	1	1	2
DPC (1:2)	0	0	0	1	0
DPC (1:3)	0	0	1	1	1
Optimized formulation	0	0	0	0	0

*Results are the mean of 3 observations

InVitro Dissolution studies

InVitro dissolution studies of the prepared ODTs were performed in 0.1N HCl using USP type II (paddle) dissolution apparatus. The dissolution rate was found to increase linearly with increasing concentration of superdisintegrant. Formulations F1, F2 and F3 which contained increasing concentrations of croscarmellose sodium have recorded drug release 70.1±1.37%, 74.5±1.05% and 80.1±1.17% respectively within 15 min. Formulations F4, F5 and F6 which contained increasing concentrations of crospovidone have recorded drug release 82.5±0.7%, 86.9±0.82% and 92.2±0.47% respectively, at the end of 15 min. Formulations F7, F8 and F9 which contained increasing concentrations of sodium starch glycolate have recorded drug release 75.2±0.35%, 77.9±0.6% and 82.8±1.45% respectively, at the end of 30 min. Formulations F10, F11 and F12 which contained increasing concentrations of low-substituted hydroxypropyl cellulose have recorded drug release 54.5±1.27%, 61.5±2% and 67±1.22% respectively, at the end of 30 min. Among all the formulations F6 shows rapid drug release 92.2±0.47% at the end of 15 min when compared to all the formulations. The rapid drug dissolution from the formulation containing CP might be due to its rapid water absorbing nature involving both capillary and swelling mechanisms resulted in easy breakdown of tablet thereby releasing the drug within a small time.

Table13: Cumulative percent drug release of Atenolol from ODTs containing varying concentrations of Croscarmellose sodium.

Time (min)	Cumulative percent drug release		
	F1	**F2**	**F3**
0	0	0	0
5	58.9±1.03	67.5±0.72	71.8±0.98
10	66.±1.86	71.5±0.8	77.1±1.76
15	70.1±1.37	74.5±1.05	80.1±1.17
20	72.6±1.35	77.8±1.53	83.2±0.81
30	75.2±0.87	80.7±1.4	86.2±0.98
40	77.7±0.96	82.5±1.33	88.5±1.6
50	79.8±1.05	85.1±1.3	91.03±0.98
60	81.6±1.2	86.6±1.8	94.4±0.6

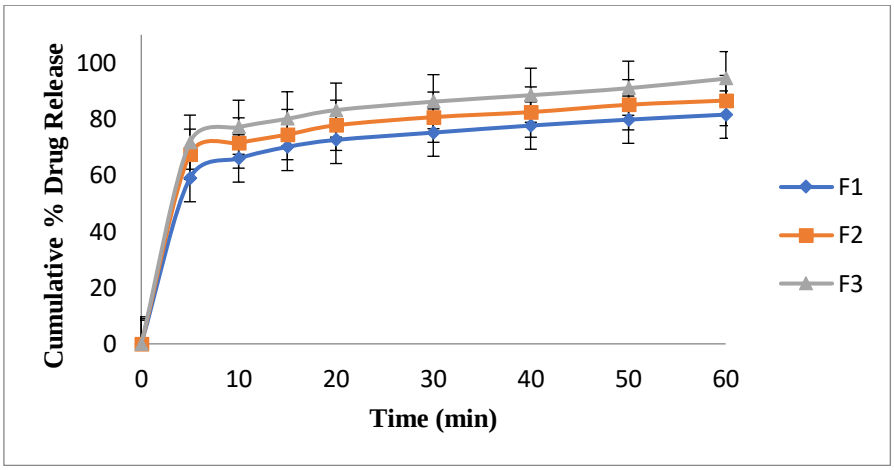

Figure 10: In-vitro cumulative percentage drug release profile of formulations with different concentrations of Croscarmellose sodium.

Table14: Cumulative percent drug release of Atenolol from ODTs containing varying concentrations of Crospovidone.

Time (min)	Cumulative percent drug release		
	F4	F5	F6
0	0	0	0
5	74.7±0.96	77.33±0.763	86±0.87
10	80.7±0.95	84.01±0.94	90.1±0.87
15	82.5±0.7	86.9±0.82	92.2±0.47
20	87.1±1.42	87.3±1.04	93.9±0.51
30	88.6±1.15	90.2±1.27	95.2±0.8
40	90.4±0.8	91.2±1.4	96.8±0.45
50	92.03±0.47	93.8±1.34	98.3±0.2
60	93.8±0.95	95.9±0.87	99.8±0.36

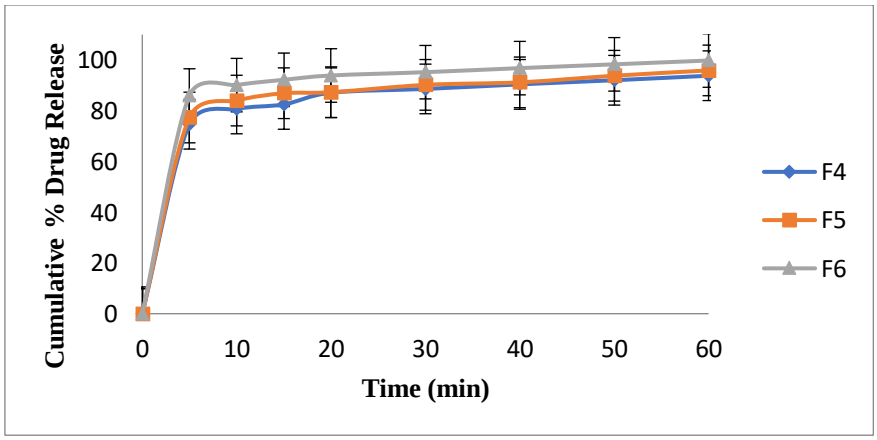

Figure 11: *Invitro* cumulative percentage drug release profile of formulations with different concentrations of Crospovidone.

Table 15: Cumulative percent drug release of Atenolol from ODTs containing varying concentrations of Sodium starch glycolate.

Time (min)	Cumulative percent drug release		
	F7	F8	F9
0	0	0	0
5	65.3±0.64	70.1±0.8	73.3±0.7
10	72.8±0.6	74.3±1.25	79.7±1.37
15	75.2±0.35	77.9±0.6	82.8±1.45
20	77.3±0.8	80.6±0.4	86.1±1.3
30	79.9±0.48	83.2±0.62	88.06±1.45
40	82.3±0.43	86.4±0.55	90.02±1.09
50	83..8±0.55	88.3±0.51	93.04±0.8
60	86.9±0.45	91.1±0.7	94.8±0.6

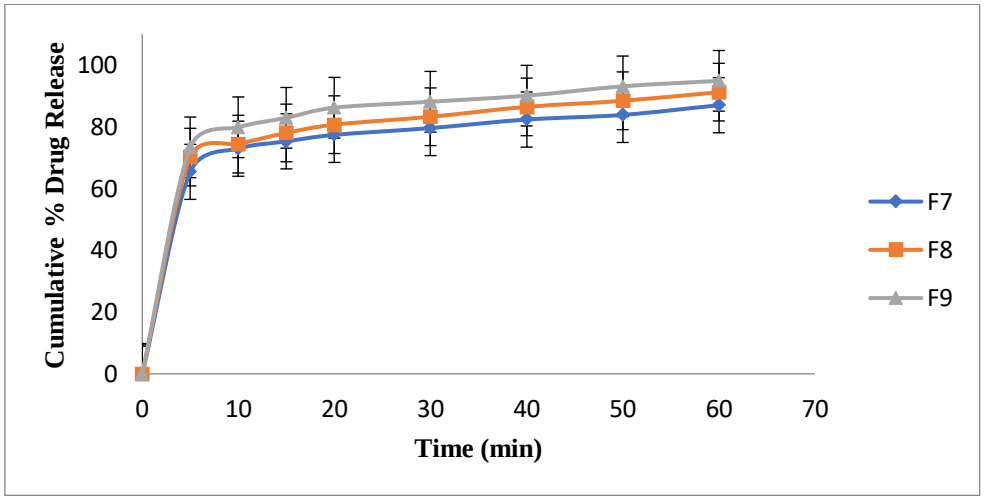

Figure 12: *Invitro* cumulative percentage drug release profile of formulations with different concentrations of Sodium starch glycolate.

Table 16: Cumulative percent release of Atenolol from ODTs containing varying concentrations of Low-susbstituted hydroxylpropyl cellulose.

Time (min)	Cumulative percent drug release		
	F10	F11	F12
0	0	0	0
5	42.5±1.2	47.9±1.15	55.9±0.96
10	48.4±1.4	55.5±1.65	60.4±1.32
15	54.5±1.27	61.5±2	67±1.22
20	58.3±1.42	65.2±1.11	71.6±1.5
30	61.4±0.7	69.2±1.06	76.4±1.05
40	64.6±2	72.4±1.3	80.3±0.8
50	67.9±1.9	75.5±1.37	83.8±1.05
60	70.5±1.15	79±1.7	85.6±1.25

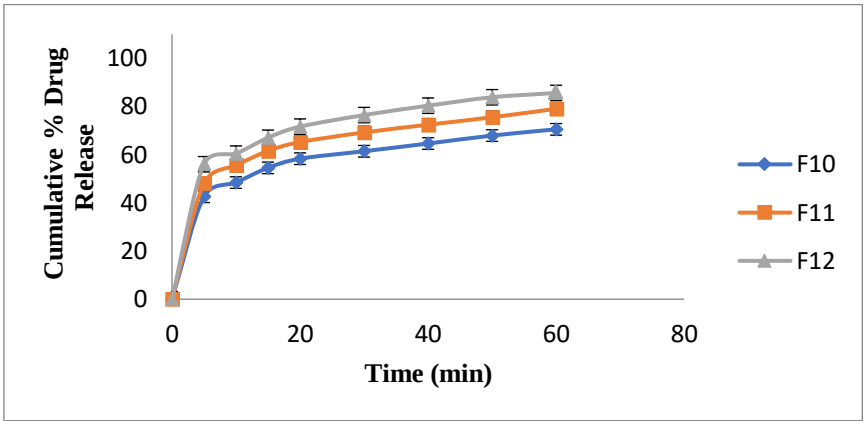

Figure 13: *Invitro* cumulative percentage drug release profile of formulations with different concentrations of Low-substituted hydroxypropyl cellulose.

CONCLUSION

Oral Disintegrating Tablets of Atenolol were formulated with an aim to improve the versatility, patient compliance and accurate dosing. The formulations ere developed with an objective to use by the pediatric and geriatric patients. Atenolol Oral Disintegrating Tablets were prepared by direct compression method using croscarmellose sodium, crospovidone, sodium starch glycolate and Low-substituted hydroxylpropylcellulose as superdisintegrants exhibited good preformulation and tabletting properties. Results demonstrated that 1:2 ratio of drug polymer complex completely masked the metallic taste of atenolol and was formulated as orally disintegrating tablets with sufficient mechanical strength and desirable taste. F6 formulation containing 6% crospovidone exhibited lowest disintegration time (22sec) and rapid drug release compared to other superdisintegrants. Taste evaluation studies revealed that the metallic taste of atenolol was completely masked by using eudragit EPO.

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