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Taste-masking assessment of orally disintegrating tablets of valsartan using ion exchange resin

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ABSTRACT

Oral disintegrating tablets are novel attractive dosage form that disintegrate or dissolve in the buccal cavity within seconds without use of water. The major drawback in designing of this dosage form is unpleasant taste of active entity. Valsartan isan anti-hypertension drug used in treatment of high blood pressure, congestive heart failure (CHF) and post-myocardial infarction (MI). It is characterized by its bitter taste which affects the patient's compliance. The aim of present research work is taste-masking assessment of orally disintegrating tablets of valsartan using ion exchange resin (indion 254). The drug was characterized according to different compendia methods, on the basis of identification by UV spectroscopy, pH, organoleptic properties and other tests. Drug-Resin compatibility and drug polymer compatibility was carried out by FTIR. The values of pre-compression parameters assessed, were within specified limits and showed good free flowing properties. The data obtained of post-compression parameters such as weight variation, hardness, friability, wetting time, water absorption ratio, content uniformity, disintegration time and dissolution was found within the prescribed limits. The F10 batch with disintegration time 20 sec and dissolution 97.46 was selected as optimized formulation. Batch F10 was also subjected to stability studies for three months and was tested for its appearance, average weight, hardness, disintegration time, percent friability and its release rate which in prescribed range and satisfactory.

1. Introduction

The term 'Oral disintegrates tablets' as give the idea in European Pharmacopoeia is defined as ''uncovered tablet for buccal cavity, where it disintegrates before ingestion''. Oral route of administration is most preferable and suitable route of drug administration as it include lots of advantages of this like ease of administration, patient compliance and accurate dosing. But there is one drawback of these dosage forms is swallowing problem for some patients of all age groups, mainly the elderly and pediatrics. Mostly new drug entity has poor water solubility and poor dissolution in GI fluids is a limiting aspect to the in vivo bioavailability after oral administration. Fast dissolving drug delivery is a significant Novel Drug Delivery (NDDS) which main purpose to improve solubility, increase efficacy and enhance safety of drug entity to formulate a dosage form for administration with better patient compliance. These tablets display a fast and spontaneous de-aggregation in the mouth, soon after it comes in contact with saliva, dissolving the active ingredient and allowing absorption through all possible membrane it comes in contact during deglutition.[1]

In the recent years, there is several new advanced technologies have been introduced for the formulation of oral disintegrates tablets with patients compliance, low disintegration time, taste masking ability and sugar free tablets for diabetic patients.[2] These techniques are based on the principles of increasing porosity and/or addition of super-disintegrates and water soluble excipients in the tablets.[3]

The formulations prepared from these techniques differ from each other on the basis of the factors like mechanical strength of final product, drug and dosage form stability, mouth feel, taste, rate of dissolution of the formulation in saliva, rate of absorption from saliva and overall drug bioavailability and polymers.[4]

Without changing its safety and efficacy, a drug's taste has to be masked and techniques are being adapted to meet this need, especially for the pediatric and juveniles patients. These are as follows: taste masking with flavors, taste masking by granulation, microencapsulation, ion exchange resins, solid dispersion method, bitterness inhibitor. When single approach for taste masking is not very successful for highly bitter drugs, using combination of various taste masking technologies is found to be a more efficient strategy.[5] Taste masking of the drug employing ion exchange resins (IER) has proved to be safe and effective method for formulation of various dosage forms.

In this paper we account Taste-masking assessment of orally disintegrating tablets of valsartan using ion exchange resin. Valsartan is an antihypertensive drug commonly used for treatment of high blood pressure, congestive heart failure (CHF) and post-myocardial infarction (MI). Valsartan suffers for poor patient's acceptability due to its bitter taste, which can be overcome by taste masking. Taste masking by ion exchange resin i.e., Indion 254 was engaged because of its efficacy and superior ability of taste masking. Ion exchange resins have been gradually more used for the taste masking of bitter taste drug and help to prepare oral disintegrates tablets.[6] Ion exchange resins are polymers that are capable of exchanging particular ions within the polymer with ions in a solution that is passed through them. This ability is also seen in various natural systems such as soils and living cells. The synthetic resins are used primarily for purifying water, but also for various other applications including separating out some elements. They are available in desired size ranges.

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Table 1 Formula of different formulations of Valsartan MDTs (mg)

Entry	Ingredients (in mg)	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9	F_{10}
1	Valsartan	40	40	40	40	40	40	40	40	40	40
2	Resin	30	30	60	60	60	60	60	80	80	80
3	Cross -povidone	6	6	6	8	8	8	10	10	12	12
5	Dry maize starch	18	-	-	21	31	30	28	19	20	25
6	Mannitol	60	80	-	-	-	-	-	-	-	-
7	MCC(rank 102)	25		40	40	40	25	40	30	27	21
8	Lactose	-	25	29	-	-	-	-	-	-	-
9	Aspartame	1	2	1.5	-	1	-	2	1	-	-
10	Sodium saccharin	0.5	-	0.5	-	-	1	-	-	-	-
11	Neotame	-	-	-	1.5	1	1	0.5	-	0.5	1
12	Flavour	2**	2*	2**	2**	2	2***	2***	2***	2***	2***
13	Magnsiumsterate	1.5	2	2	1.5	1.5	2	1.5	1.5	1.5	2
14	Aerosil	3	3	3	2	2	2	2	1	2	2
15	Citric acid	3		3	2	2	2.5	2	2	2	2
16	Mono sod.citrate	-	-	3	2.5	-	-	-	-	-	-
17	Sodium citrate tribasic dihydrate	-	-	-	-	-	2.5	2	3	3	3
*	Total	190	190	190	190	190	190	190	190	190	190

Flavor----strawberry, orange**, pineapple***.

Table 2 Evaluation of Precompressed Powder Blend

Entry	Bulk density	Tapped density	Carr's index	Hausner ratio	Angle of repose
F1	0.4175	0.4830	14.54	1.17	32.18
F2	0.4278	0.4870	12.s5	1.13	33.57
F3	0.4188	0.4790	12.56	1.14	34.42
F4	0.4388	0.4971	11.72	1.13	31.37
F5	0.4273	0.4907	12.92	1.14	32.29
F6	0.4232	0.4842	12.59	1.14	31.19
F7	0.4188	0.4780	12.34	1.14	31.21
F8	0.4206	0.4750	11.45	1.12	31.09
F9	0.4219	0.4778	11.69	1.13	31.27
F10	0.4246	0.4825	12.11	1.13	32.25

Bitter cationic drugs can get adsorbed on to the weak cationic exchange resins of carboxylic acid functionally to form the complex which is not bitter. Further Drug-Resin complex can be formulated as lozenges, chewing gum, suspension or dispersible tablet and mask the taste.[7]

2. Result and discussion:

The formulation of oral disintegrating tablet was made by using valsartan–resin complex. Batches F_1– $F_{10}$was prepared by direct compression to select disintegrate, from the results. It can be concluded that the tablets containing crospovidone exhibit quick disintegration time. From the results it was obvious that the optimum concentration of crospovidone might be less than 10%. Batches F8 (39 sec), F9 (33sec) and F10 (20sec) exhibited decrease in disintegration time and wetting time (24–26 sec).But F10 had shown more decrease in disintegration time and wetting for this reason batch F10 was selected. The tablet blend of all the batches were evaluated for different derived properties viz. angle of repose (between 32.18 and 32.25), Bulk density (between 0.41 and 0.42 gm/cm^3), Tapped Density (0.483–0.482 gm/cm^3), Compressibility index (between 14 and 12, hausner ratio (between 1.17 and 1.13) and flow ability. The results of angle of repose and compressibility indicated that the flow ability of blend is significantly good. Oral disintegrating tablets were pre-pared in batches F1–F10 and evaluated for tablet properties like, weight variation, hardness, friability, wetting time, water absorption ratio, content uniformity, disintegration time and dissolution.

Table 3 Physical evaluation of MDTs Valsartan

Entry	Weight Variation (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Wetting time (seconds)	In-vitro disintegration time (seconds)	Percent drug content (%)
F1	186-193	2.82	1.8	0.0495	64	58	101
F2	185-192	2.82	1.6	0.0462	75	67	99.50
F3	187-194	2.72	2	0.1126	80	72	98.70
F4	187-192	2.72	2	0.0500	60	50	101
F5	185-192	2.82	1.8	0.3980	56	45	99
F6	188-195	2.84	1.6	0.4960	51	47	98
F7	186-193	2.72	2	0.0500	37	29	98
F8	185-194	2.82	1.8	0.3980	39	30	99
F9	188-195	2.89	2.2	0.431	33	24	99
F10	187-194	2.81	2.3	0.465	26	20	99

Table 4 Dissolution study of different batches

Time(min)	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9	F_{10}
15	85.50	84.93	84.90	83.25	83.25	86.27	86.05	82.22	86.26	86.94
30	94.69	95.33	96.67	94.29	94.64	95.66	93.08	94.57	94.72	96.75
45	95.37	96.34	97.03	95.33	95.34	96.01	96.43	95.98	96.07	97.42

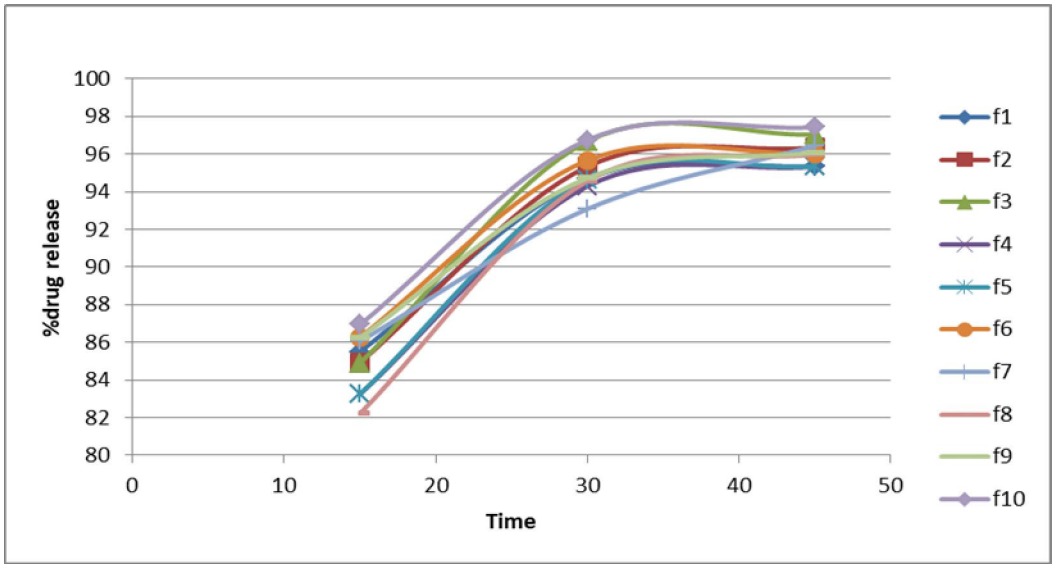

Fig 1. Dissolution study of different batches

All the tablets passed weight variation test as the percent weight variation was within the pharmacopoeia al limits. Hardness were shown in the range of 1.8–2.3 kg/ cm^2 in all the formulations which indicated good mechanical strength with an ability to withstand physical and mechanical stress conditions while handling. In all the formulations, the friability value was less than 1% and meets the official limit. The results of disintegration of all the tablets were found to be within prescribed limits and satisfied the criteria of oral disintegrating tablets. The values were found to be in the range of 0.049–0.46. The percentage drug content of all the tablets was found to be between 101 and 99 of valsartan which was within acceptable limit. All the tablets prepared were subjected for release profile. The tablets prepared from crospovidone i.e., F_1– F_{10}showed a drug release between 82.22 and 97.42. Results for hardness, disintegration time, dissolution and content uniformity show no appreciable change up to 3 months of accelerated stability studies.

3. Conclusion:

Great deal of attention is drawn by oral disintegrating tablets in last few years. Because of the increase in the average life extent and the decline, with age, in swallowing ability, oral tablets administration to patients is momentous problem and has become

the objects of public attention. Dosage forms that can be suspended or dissolved in mouth with water for swallowing easily are desired candidate for the geriatric and pediatric population. Organoleptic characteristics like taste and odour are required features in evaluating the consumer acceptability, thereby are needed for their success in the market.

In this article ion exchange resin are used for taste masking of oral disintegrating tablets which have shown preferred results. In this present work ten formulations are prepare by complexation with ion exchange resin which resulted in change of crystalline form of drug to amorphous form which has improved the dissolution properties of valsartan.

4. Materials and methods

4.1. Materials

All materials used in the present research were commercial samples. Active agent: Valsartan (Morepen Lab. Ltd), Resin (Indion 254) (Morepen Lab. Ltd), microcrystalline cellulose (Morepen Labs), Crospovidone (Paracol corporation), dry maize starch, mannitol, lactose, aspartame and magnesium stearate (Amishi Chemicals Ahmedabad), aerosol, citric acid, sodium citrate tribasic dehydrate-2 are gift sample from Morepen Lab. Ltd. All other reagents were of analytical grade.

4.2. Preparation of tablets

The preparation of tablets was carried out after the analysis of drug samples, ion exchange resins, mixture formation and their analysis, drug loading studies, formulation and evaluation of Tablets.[8]

4.3. Analysis of Valsartan

The Valsartan was characterized according to different analytical methods and was found to be white to white crystalline powder with characteristic odour. Found to have a melting point in range of 116–117 ^{o}C and a pH of 4-8, λ_{max} of 250 nm, and all the findings matched the official reports.

4.4. Scanning of Valsartan.

The λmax of drug had been determined by subjecting the stock solution (100 mg of valsartan was accurately weighed and transferred into a 100 ml volumetric flask. The drug was then dissolved in 20 ml of methanol and diluted up to the mark with pH 6.8 phosphate buffer solution) with) to the U.V. scan between 200-400 nm. The wavelength for maximum absorbance was noted from the scan at 250 nm (because of sharp and intense peak) in pH 6.8 phosphate buffer which confirms to the reported value.

4.5. Preparation of standard calibration curve using with pH 6.8 phosphate buffer solution

A standard curve of valsartan(using 100µg/ml) was obtained by measuring absorbance of various aliquots at 250 nm.For thestandard curve, 100 mg of valsartan was accurately weighed and transferred into a 100 ml volumetric flask then 10 ml was pipetted out and diluted to 100 ml using pH 6.8 phosphate buffer solutions.

Different aliquots containing 2, 4, 6, 8, 10, 12 & 14 µg/ ml of valsartan were prepared. The absorbance of dilutions was measured against pH 6.8 phosphate buffer solutions as a blank at 250 nm using UV/visible spectrophotometer. The plot of absorbance Vs concentration was plotted and subjected to linear regression analysis.

4.6. Characterization of drug and excipients

4.6.1. Drug-excipient compatibility studies

The physiochemical Compatibility of the valsartan with indion 254, after that combination of the valsartan and super disintegrates and excipients were carried out to investigate the changes in chemical composition of the drug after combining it with the excipients.

The drug-polymer compatibility was studied by FTIR (Shimadzu IR Affinity-I) spectrophotometry. The mixture of drug and potassium bromide was ground into a fine powder using mortar Pestle and then compressed into a KBr discs in a hydraulic press at a pressure of 75 Kg/cm2. Each KBr disc was scanned 45 times at a resolution of 2 cm–1. The characteristic peaks were recorded.

4.6.2. TLC Method:

The drug polymer compatibility was also studied by densitometry TLC evaluation using aluminum foil plates percolated with silica gel (60G F254) with Ethyl acetate: chloroform: glacial acetic acid,(8:2:0.2 v/v as mobile phase.

4.6.3. HPLC analysis

The quantitative analysis of drugs was performed using an HPLC (Waters 515 series, water corporation, USA), For HPLC, mobile phase, water: acetonitrile: glacial acetic acid (500:500:01) was filtered and degassed. The injection volume was injected 20µl with a flow rate of 1.0ml/min. Detection was carried out at 273 nm. At column temperature 250^{o}c and run time set at 10 minutes.

4.7. Preparation of drug–resin complex (DRC)

In batch process, there is different ratio of Drug: Resin (1:0.75, 1:1, 1:1.5, and 1:2), Beaker containing deionized watermix with resin and stirred with mechanical stirrer for 30 min accurately weighed of valsartan was added and stirred for 2 hours. The mixtures were filtered and residue was washed with deionized water. DRC was then washed with sufficient quantity of deionized water for three times to remove loosely adsorbed drug from resinate surface. DRC was allowed to dry at room temperature and was stored in tightly closed container and used in further studies.

4.8. Formulation of oral disintegrating tablets

Valsartan tablets were prepared according to the formula given in (**Table 1**). A total number of ten formulations were prepared. All the ingredients were passed through 40 mesh sieve separately and collected. The ingredients were weighed and mixed in a geometrical order. All the sifted ingredients were then weighed individually for each batch using electronic weighing balance. The weighed ingredients were then transferred to a laboratory mixer in a sequential manner. First the treated drug and resin complex was mixed with micro crystalline cellulose and maize starch and then other excipients were added.

Table 5 Observation of parameters for the stability studies at the accelerated conditions (40^0C ±2 ^{0} C/75%±5% RH)

	Time			
Parameters	**Days**	**30 Days**	**60 Days**	**90 Days**
Appearance	No change	No change	No change	No change
Average weight	191	191	192	192
Hardness (kg/cm^2)	2	2	1.8	1.8
Disintegration time(seconds)	20	20	20	20
Percent friability	0.465	0.465	0.465	0.465

Table 6 Release kinetics data of optimized batch (F_{10}) after 30, 60 & 90 days

		Percent drug release			
Entry	**Time (min)**	**0 Days**	**30 Days**	**60 Days**	**90 Days**
1	15	86.94	84.43	84.20	84.01
2	30	96.75	94.21	93.92	93.62
3	45	97.42	96.03	95.92	95.63

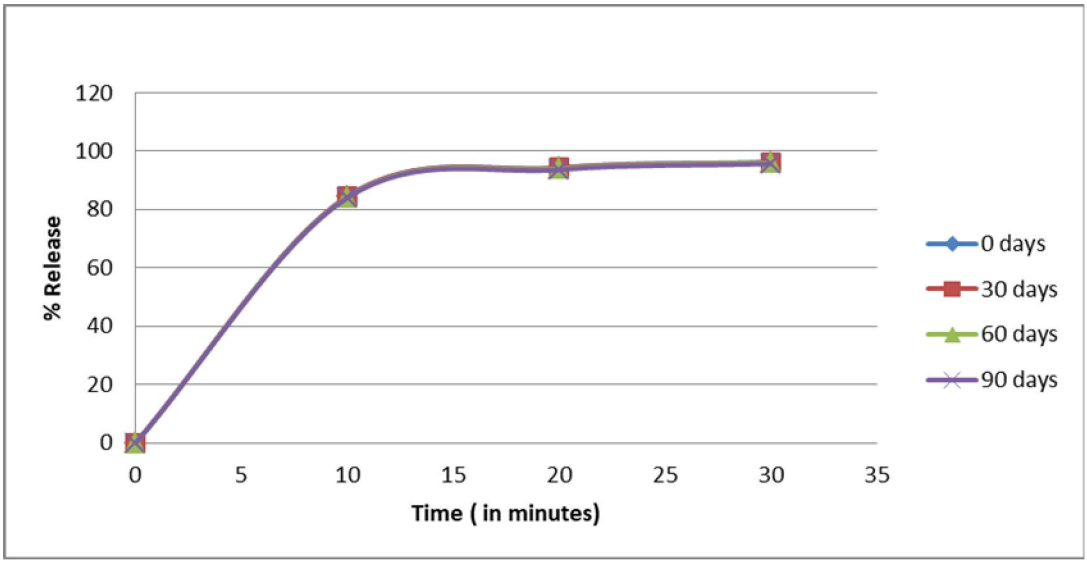

Fig 2. Release kinetics of F_{10} in stability testing conditions

Talc and magnesium stearate were added few minutes before the start of compression. The tablet was punched by using 9mm punches to get a tablet of 190 mg weight. Before tablet preparation, the powder mixture of all formulation were passed to pre-compression parameter like bulk density, tapped density, angle of repose, Carr's index, hausner ratio, and compressibility and flow ability. The oral disintegrating tablets prepared subjected to post-compression parameters like, content uniformity, hardness, friability, weight variation, dissolution and in vitro disintegration. Batches were prepared by direct compression method. Direct compression is the preferred method for preparation of tablets. Current usage of the term ''direct compression'' is used to define the process by which tablets are compressed from the powder blends of active ingredient/s and suitable excipients. No pretreatment of the powder blends by wet or dry granulation is involved.

4.9. Evaluation of blend for oral disintegrating tablets

4.9.1. Angle of repose (θ)

The friction forces in a loose powder were measured by the angle of repose (θ), an indicative of the flow properties of the powder. It 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 cm and r is the radius in cm.

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 (Table 2).

4.9.2. 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. The bulk density was calculated according to the formula mentioned below. It was expressed in g/ml and given by

$$Db = M/Vb$$

where, M the mass of powder and Vbbulk volume of the powder.

4.9.3. 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 1000 times and the tapped volume was noted if the difference between these two volumes less than 2%. If it was more than 2%, tapping continued for 1250 times and tapped volume was again noted. It was expressed in g/ml and given by

$$Dt = M/VT$$

Where M the mass of powder and Vt the tapped volume of the powder.

3.9.4. Carr's index (or) % compressibility

It indicated powder flow properties. It was expressed in percentage and given by:-

$$I = Dt - Db/Dt * 100$$

where Dt; the tapped density of the powder and Db; the bulk density of the powder.

4.9.5. Hausner ratio

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

$$Hauser\ ratio = Dt/Db$$

where, Dt; the tapped density and Db; the bulk density. Lower hausner ratio (<1.25) indicated better flow properties than higher ones (>1.25).

4.9.5.1. Angle of repose

The flow characteristics are measured by angle of repose. Improper flow of powder is due to frictional forces between the particles. These frictional forces are quantified by angle of repose. Angle of repose is defined as the maximum angle possible between the surface of a pile of the powder and the horizontal plane.

$$\tan h\frac{1}{4} - h/r$$

$$h\frac{1}{4}tan^{-1} - h/r$$

4.10. Evaluation of tablets

The formulated oral disintegrating tablet were evaluated for different parameters like, weight variation hardness,[9] friability, wetting time,[4] water absorption ratio,[10] content uniformity and dissolution.[11]

4.10.1. Thickness

The thicknesses of the compressed tablets were measured by using Vernier callipers.

4.10.2. Weight variation:

The compressed tablets were tested for weight uniformity. For this 20 tablets accurately weighed. After the obtained weight, average weight was calculated. Each tablet's weight was then

$$\%\ Weight\ variation = \frac{Average\ weight - Individual\ weight}{Average\ weight} * 100$$

compared with average weight to determine whether it was within acceptable limits or not.

4.10.3. Hardness

Hardness of tablets was measured using Pfizer type hardness tester. Three tablets were selected from each formulation randomly and their hardness was measured. The means of hardness values were calculated.[4]

4.10.4. Friability

Friability of the tablets was determined by using Roche friabilator. The weight of 20 tablets (initial weight) was subjected to friabilator at 25 revolutions per 4 min. Tablets were then dedusted, reweighed (final weight) and percentage loss was calculated. Friability is obtained by the following formula:

$$\%Friability = \frac{Initial\ weight - Final\ Weight}{Initial\ weight} * 100$$

4.10.5. Wetting time and water absorption ratio:

A double folded tissue paper was placed in a Petri dish. 6 mL of water containing a water-soluble dye (eosin) was added to the Petri dish. A tablet (pre-weighed) was carefully placed on the surface of tissue paper.

The time required for water to reach the upper surface of the

tablet was noted as the wetting time. The wetted tablet was then weighed and the water absorption ratio (R) was determined by using the equation:

$$R = 100\ (Wb - Wa)/Wb$$

where Wa and Wb are the weights of tablet before (dry weight and after water absorption wet weight) respectively.

4.10.6. In vitro disintegration test:

In vitro disintegrating time was determined by using disintegration test apparatus without disk for six tablets. The disintegration medium was 900 mL of distilled water kept at (37.0°C) and stirred at a rate of (30) r/min. The time was considered in seconds for complete disintegration of the tablet with clear mass remains. (**Table 3**)

4.10.7. Dissolution studies:

In-Vitrodrug release studies were carried out by using USP (TDT 06L) Type II (paddle type) dissolution test apparatus at 50 rpm using pH 6.8 phosphate buffer as dissolution media maintained at the temperature of 37±0.5°C. Samples were withdrawn at specific time intervals and replaced with fresh media and filtered. The amount of drug dissolved was determined by spectrophotometrically at 250 nm (**Table 4**). The experiments were conducted in triplicate. The comparative results are shown as (**Fig.1**).

4.10.8. Stability Study:

The optimized formulations were packed suitably and kept in stability chamber at accelerated conditions (40 ^{0}C± 2 ^{0}C/75%±5%RH) for a period of three months (**Table 5**). The samples were analyzed at 30, 60 and 90 days for different physiochemical parameters (**Table 6**) and in-vitro drug release (**Fig. 2**).

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