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THE PHARMA RESEARCH

An International Journal of Pharmacy Research

VALSARTAN MDT; A PROMISING DOSAGE FORM TO TREAT HYPERTENSION AND CONGESTIVE HEART FAILURE

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ARTICLE INFO

Published on: 15 June 2018
ISSN: 0975-8216

Keywords:
Valsartan, MDT, ORO, Dispersible, Congestive, Heart, Failure, Hypertension

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ABSTRACT

Aim: The objective of the present work was to develop mouth dissolving tablet of Valsartan in order to attain instantaneous pre gastric release of the drug in upper gastro intestinal tract which resulted enhanced bioavailability of the drug bypassing the first pass metabolism. **Experiment:** present worker prepared ten batches of oral disintegrating tablet of Valsartan by adopting superdisintegrant addition method. Various pre-compression physiochemical parameters of formulation blends were analyzed and obtained results were angle of repose (31-34), bulk density (0.41-0.43), tapped density (0.47-0.49), carr's index (11-14) and hausner ratio (1.11-1.17). The prepared tablets were evaluated for various post-compression parameters and results depicted friability (0.04-0.40), hardness (1.6-2.3), in-vitro disintegration time (20-72) and percent drug content (98-101). The accelerated stability study was performed on the finalized formulation (F_{10}) as per the ICH guidelines at accelerated conditions (40^0**±**2^0C, 75%**±**5% RH) which confirmed the formulation as stable with no physical change and also there was no significant reduction in drug contents. **Result:** The best drug release profile were seen with formulation f_{10} i.e. 97.42%, in pH 6.8 phosphate buffer solution while in simulated salivary fluid it was found to be 96.81%. An ex-vivo study was carried out on this optimized batch in Franz Apparatus and the results revealed the permeation of 79.0825%. **Conclusion:** From study, it was concluded that oral disintegrating tablet formulation of Valsartan could be successfully formulated and would be used as novel drug dosage form with improved patients compliance and enhanced bioavailability.

INTRODUCTION

Amongst the various routes of drug delivery, oral route is perhaps the most preferred to the patient and the clinician's alike.[1] The most common way to give medications is orally or by mouth, in which the patient swallows. The enteral route is used primarily for convenience, economy, stability and patient acceptance. In this route of delivery, the medication must reach the intestine where it is broken down, absorbed across the intestinal wall, picked up in the blood stream and delivered to its intended target. These steps, however, take time up to 30 to 45 minutes between the administration of the medication and its therapeutic effect. However, peroral administration of drugs has disadvantages such as hepatic first pass metabolism and enzymatic degradation within the GI tract that prohibits oral administration of certain classes of drugs especially peptides and proteins.

Consequently, other absorptive mucosae are considered as potential sites for drug administration. Oral transmucosal drug delivery bypasses first pass effect and avoids presystemic elimination in the GI tract. These factors make the oral mucosal cavity a very attractive and feasible site for systemic drug delivery.[2, 1]

United States of America food and drug administration (FDA) defines ODT as "A solid dosage form containing medicinal substances or active ingredients which disintegrate rapidly usually within a matter of seconds when placed upon the tongue".

Such tablets readily dissolve or disintegrate in the saliva generally within <60 seconds.[7]

Recent advances in Novel Drug Delivery Systems (NDDS) aim at formulating a dosage form, conveniently administered so as to achieve better patient compliance. Pharmaceutical technologists have put in their best efforts to develop Oral Disintegrating Tablets.

Among the dosage forms developed to facilitate ease of medication, oral disintegrating tablet is one of the most widely employed commercial products.[4]

As our society is becoming increasingly aged, the development of Fast- or mouth dissolving tablets have been formulated for pediatric, geriatric, bedridden patients and for active patients who are busy, traveling and may not have access to water.

Within the oral mucosal cavity, delivery of drugs is classified into three categories:

- **Sublingual delivery**: intended for administration through the membrane of the ventral surface of the tongue and the floor of the mouth. The sublingual mucosa is relatively permeable giving rapid absorption and acceptable bioavailabilities of many drugs and is convenient, accessible and generally well accepted.
- **Buccal delivery**: administered through the buccal mucosa mainly composed of the lining of the cheeks.
- **Local delivery**: meant for administration through all areas other the former two regions. Local delivery to tissues of the oral cavity has a number of applications including the treatment of toothaches, periodontal diseases, bacterial and fungal infections, aphthous and dental stomaitis and in facilitating tooth movement with prostaglandins.[3]

Tablets and capsules are the most popular dosage forms except for persons having 'Dysphagia' or difficulty in swallowing, also associated with a number of conditions like: Parkinsonism, Motion sickness, Unconsciousness, Elderly patients, Children, Mentally, disabled persons and Unavailability of water.

Mouth dissolving drug delivery systems (MDDDS) are a new generation of formulations which combine the advantages of both liquid and conventional tablet formulations and at the same time offer added advantages over the traditional dosage forms.

Ideal properties of ODT:[6, 4]

An oral disintegrating tablet should

- Not require water or other liquid to swallow.
- Easily dissolve or disintegrate in saliva within a few seconds.
- Have a pleasing taste.
- Leave negligible or no residue in the mouth when administered.
- Be portable and easy to transport.
- Be able to be manufactured in a simple conventional manner within low cost.
- Be less sensitive to environmental conditions like temperature, humidity etc.

Characteristics of Fast Dissolving Delivery Systems:[7]

- Ease of administration
- Taste of the medicament:
- Hygroscopicity:
- Fri Mouth feel

Advantages of Oral Disintegrating Tablets:

1. Ease of administration to patients who cannot swallow, such as the elderly, stroke victims and bedridden patients; patients who should not swallow, such as renal failure patients; and who refuse to swallow, such as paediatrics, geriatric and psychiatric patients.
2. Patient's compliance for disabled bedridden patients and for travelling and busy people, who do not have ready access to water.
3. Good mouth feel property of Oral disintegrating drug delivery system helps to change the basic view of medication as "bitter pill", particularly for paediatric patients due to improved taste of bitter drugs.
4. Convenience of administration and accurate dosing as compared to liquid Formulations.
5. Benefit of liquid medication in the form of solid preparation.
6. More rapid drug absorption from the pre-gastric area i.e. mouth, pharynx and esophagus which may produce rapid onset of action
7. Pregastric absorption can result in improved bioavailability, reduced dose and improved clinical performance by reducing side effects.

Main ingredients used in preparation of ODT:

Valsartan ,Resin Cross –povidone LactoseDry maize starch, Mannitol, MCC(rank 102), Aspartame , Sodium saccharin Neotame Mono sodium citrate Flavour, Magnsium sterate, Aerosil Citric acid, Sodium citrate tribasic dihydrate-2Pvp k-30

Superdisintegrants: [10, 5]

In many orally disintegrating tablet technologies based on direct compression, the addition of superdisintegrants principally affects the rate of disintegration and hence the dissolution. Presence of other formulation ingredients such as water-soluble excipients and effervescent further hasten the process of disintegration.

MATERIALS AND METHODS:

Various materials i.e. drug sample, additives etc were obtained from different reputed companies as summarized below:

Valsartan, Indion 204, Pharmatose Dcl -15 , Maize Starch, Mannitol, Aspartame, Flavour , Sodium citrate tribasic dihydrate-2 (MOREPEN LAB.Ltd, India), Microcrystalline Cellulose, Accent Microcell Industries (Ahmadabad), Crosspovidone (Paracol Corporation), Magnesium Stearate, (Amishi Chemicals Ahmedabad), Sodium saccharin (Om Pharmaceutical Industries), Citric acid, (Preecheza Pharmaceuticals), Neotame (Golcha Assosiates Ltd), Aerosil (Gujarat Alkalies and Chem Ltd., Gujarat).

Experimental Work:

Prepration of simulated salivary fluid:[12]

To prepare simulated salivary fluid, a 5% mucin solution was first prepared by adding 200ml of deionized water to 10 gm of mucin & stirring the mixture until dissolved completely. Later on following ingredients such as $NaNo_2$, $Mgcl_2$, $Cacl_2.2H_2O$, Nacl KH_2PO_4 K_2HPO_4, Kcl, $NaHCo_3$, Thimerosol, Amylase, Antipain were mixed about 800 ml of deionized water with slow stirring in another volumetric flask.

FORMULATION DESIGN OF ORAL DISINTEGRATING TABLETS:

FORMULATION DESIGN OF ORAL DISINTEGRATING TABLET:

S.no.	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	Magnsium sterate	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	**-**	-	**-**	**-**	**-**	2.5	2	3	3	3
	TOTAL	**190**	**190**	**190**	**190**	**190**	**190**	**190**	**190**	**190**	**190**

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

Drug polymer compatibility study:

FTIR analysis: [13, 11]

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/cm^2. Each KBr disc was scanned 45 times at a resolution of 2 cm^{-1}. The characteristic peaks were recorded.

TLC Method:

The drug polymer compatibility was also studied by densitometry TLC evaluation using aluminum foil plates precoated with silica gel (60G F_{254}) with Ethyl acetate: chloroform: glacial acetic acid, (8:2:0.2 *v/v)* as mobile phase.

METHOD OF FORMATION OF DRUG: RESIN COMPLEX.[14]

Deionized water + Resin
↓ stirring with mechanical stirrer
Added valsartan
↓ stirring
Stirring continued upto 2hrs.
↓ dried
Dried at 50^{0}c. Dried complex was used for formulation of ODT.

Schematic representation for preparation of VALSARTAN: RESIN complex

Preparation of formulation blend:

All the ingredients were sieved individually through sieve no.40 to ensure the absence of any unwanted particulate matter and to break up the lumps, if present, for the ease of mixing and to ensure the proper flow. 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. Talc and magnesium stearate were added few minutes before the start of compression.

- **Pre-compression evaluation of formulation blend.**
- **Angle of repose (¾):**[15]
- The friction forces in a loose powder were measured by the angle of repose **(¾)**, an indicative of the flow properties of the powder. It is defined as maximum angle possible between the surface of the pile of powder the horizontal plane

$$\tan (¾) = h / r$$
$$(¾) = \tan^{-1} (h / r)$$

Where, **(¾)** is the angle of repose, h is the height in cm and r is the radius in cm.

Bulk Density (Db):

It is the ratio of total mass of powder to its bulk volume. 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 Vb bulk volume of the powder.

Tapped Density (Dt):

It is the ratio of total mass of the powder to its tapped volume. Volume was measured by tapping the powder for 1000 times and it was noted if the difference between these two volumes lied less than 2%. If it was more than 2%, tapping continued for 1250 times and tapped volume was again noted.

Tapped density was expressed in g/ml and given by

$$Dt = M / Vt$$

Where M: the mass of powder, Vt: the tapped volume of the powder.

Carr's index (or) % compressibility: [16]

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

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

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

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

$$\frac{Dt}{}$$

$$\text{Hausner ratio} = \frac{\text{Dt}}{\text{Db}}$$

Where, Dt; the tapped density and Db; the bulk density.

Lower hausner ratio (<1.25) indicated better flow properties than higher ones (>1.25).

PREPARATION OF ODT's:

The oral disintegrating tablets of valsartan were prepared by compressing the powdered formulation blend by direct compression method using automatic 16 stations punching machine.

EVALUATION PARAMETERS OF ODT's.

The formulations were evaluated for the following evaluation parameters.

Tablet weight variation-[17]

Tablet thickness-

Hardness

Friability

Drug content uniformity

Wetting time:

In-Vitro Dissolution Studies:

Ex-VIVO STUDY:

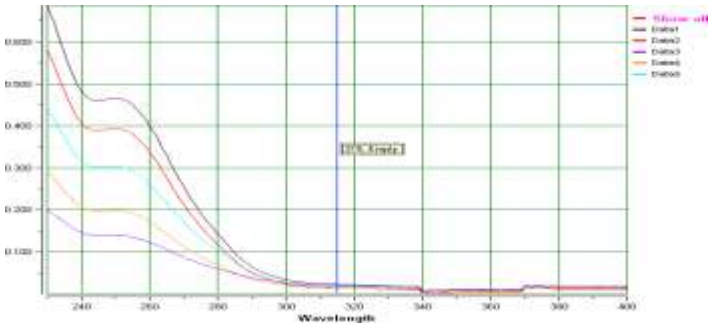
Stability Study: [18]

Result and Discussion:

Experimental studies

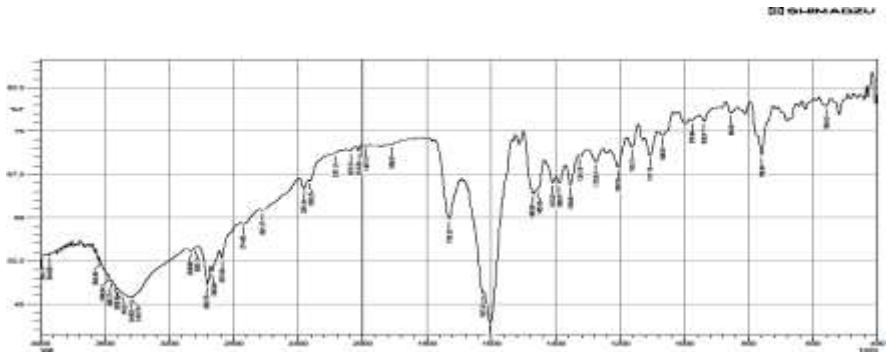
Validation of λmax.

The λmax of drug had been determined by subjecting the stock solution 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).



DRUG-EXCIPIENT COMPATABILITY STUDIES:

FTIR Analysis:



EVALUATION PARAMETERS OF TASTE MASKED FORMULATION

Pre-compression parameters like bulk density, tapped density, carr's index, hausner ratio and angle of repose for samples of formulation blend (F_1-F_{10}) were determined and found in the range of 0.41-0.43, 0.47-0.49, 11-14, 1.11-1.17 and 31-34 respectively.

Results of pre-compression parameters.

SNO	FORMULATED CODE	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9	F_{10}
1	**Bulk density**	0.4175	0.4278	0.4188	0.4388	0.4273	0.4232	0.4188	0.4206	0.4219	0.4246
2	**Tappd density**	0.4830	0.4870	0.4790	0.4971	0.4907	0.4842	0.4780	0.4750	0.4778	0.4825
3	**Carr's index**	14.54	12.15	12.56	11.72	12.92	12.59	12.34	11.45	11.69	12.11
4	**Hausner ratio**	1.17	1.13	1.14	1.13	1.14	1.14	1.14	1.12	1.13	1.13
5	**Angle of repose**	32.18	33.57	34.42	31.37	32.29	31.19	31.21	31.09	31.27	32.25

Post compression parameters:

The samples from each batch of tablet formulation were evaluated for the post compression parameters such as weight variation, thickness, hardness, friability, wetting time, In-vitro disintegration time & persent drug content. The results inferred weight-variation, thickness, hardness, friability, wetting time, disintegration time & percent drug content in the range of 185-195, 2.7-2.8, 1.6-2.3, , 0.04-0.4, 26-80, 20-72 & 98-101 respectively.

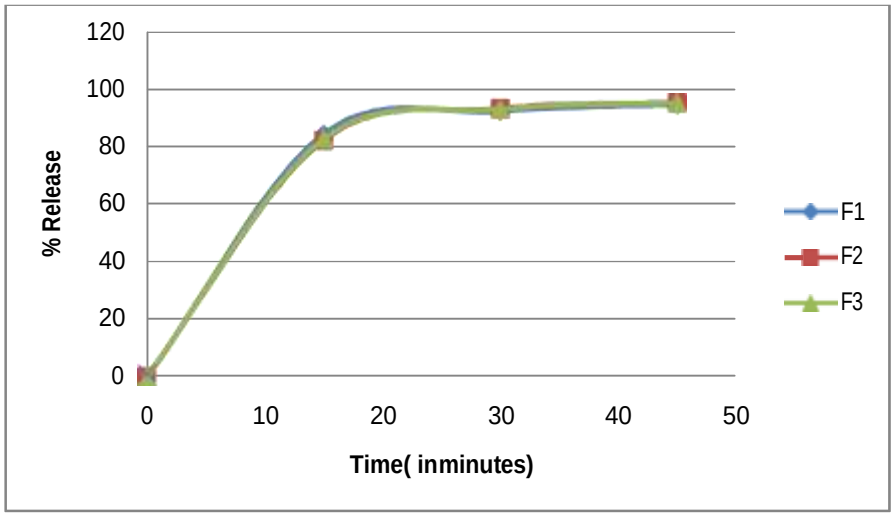
Results of post-compression parameters for batches F_1-F_{10}

S.N	**parameters**	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9	F_{10}
1	Weight variation(mg)	186-193	185-192	187-194	187-192	185-192	188-195	186-193	185-194	188-195	187-194
2	Thickness(mm)	2.82	2.82	2.72	2.72	2.82	2.84	2.72	2.82	2.89	2.81
3	Hardness (kg/cm^2)	1.8	1.6	2	2	1.8	1.6	2	1.8	2.2	2.3
4	Friability (%)	0.1126	0.0462	0.0495	0.0500	0.3980	0.4960	0.0500	0.3980	0.431	0.465
5	Wetting time(s)	64	75	80	60	56	51	37	39	33	26
6	DT	58	67	72	50	45	47	29	30	24	20
7	% drug content	101	99.50	98.70	101	99	98	98	99	99	99

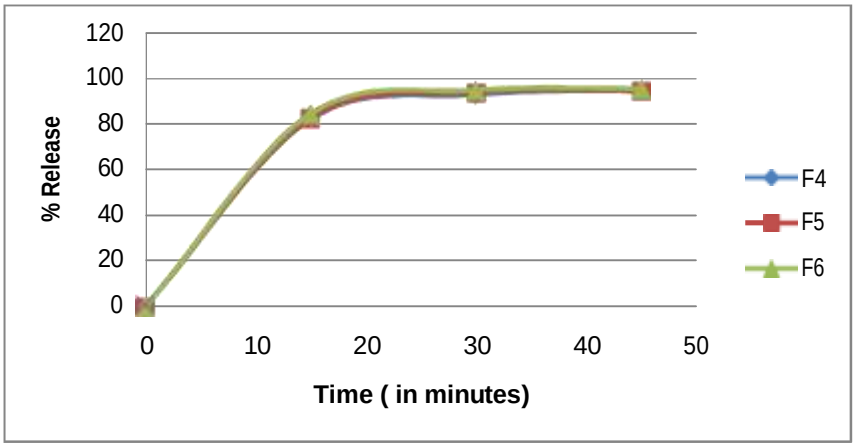
In-vitro dissolution profile of formulation in simulated salivary fluid:

S no.	Time (min)	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9	F_{10}
		% Release									
1.	15	84.39	82.31	82.90	81.99	82.33	84.29	85.01	80.11	84.22	85.31
2.	30	92.32	93.33	93.17	92.84	93.64	94.66	92.22	92.57	93.71	94.71
3.	45	94.66	95.31	95.31	94.66	94.31	95.34	95.41	93.71	95.64	96.81

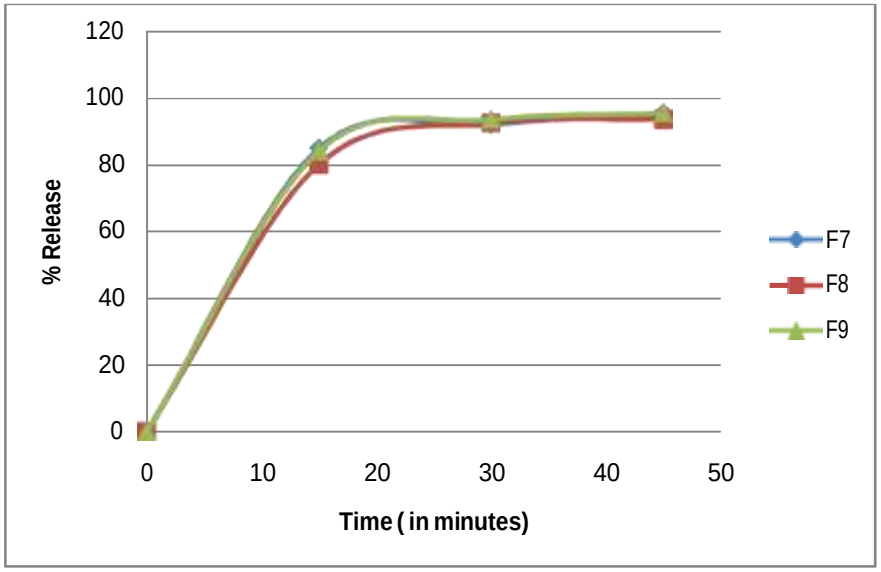
Relaease kinetic data of formulation F_1- F_{10} in simulated salivary fluid:



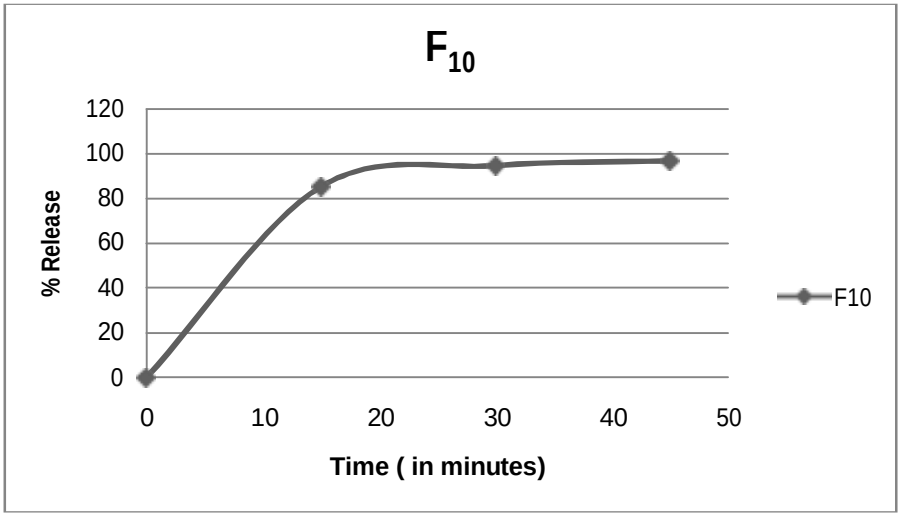
Comparative release profile of batches F_1, F_2 and F_3 in simulated salivary fluid.



Comparative release profile of batches F_4, F_5 and F_6 in simulated salivary fluid.



Comparative release profile of batches F_7 F_8 and F_9 in simulated salivary fluid.



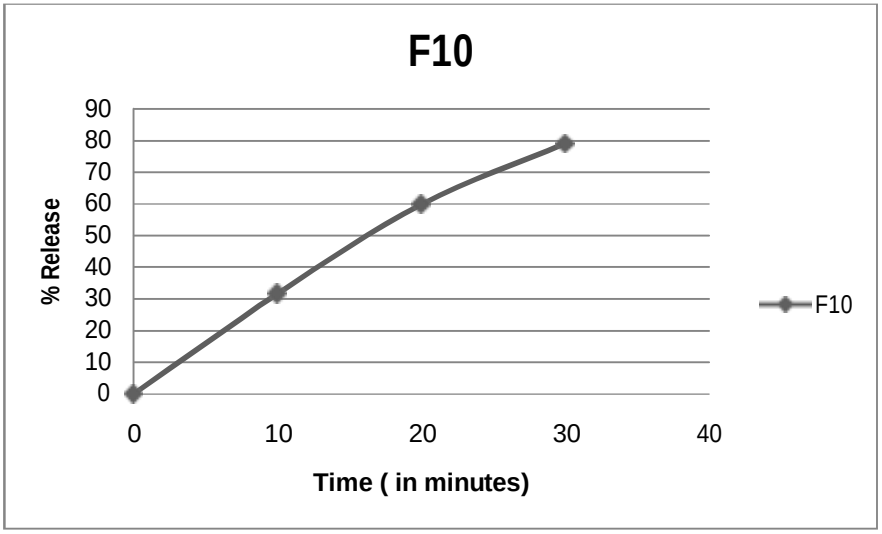
Release profile of batch F_{10} in simulated salivary fluid.

Ex-vivo study: ex-vivo studies were performed for the best optimized batch (with best taste masking and dissolution profile). Study was performed on **Franz Apparatus** and cock pouch was utilized as the permeable membrane. Simulated salivary fluid was used for the experiment.

Ex-vivo evaluation of optimized Formulation (F_{10}).

Release kinetics of (F_{10}) in ex-vivo study:

S.no.	time	Conc (microgram)	Conc (mg)	cum	% release
1	15	1269.474	1.269	12.66	31.65
2	30	2267.368	2.267	23.936	59.84
3	45	2810.526	2.810	31.633	79.0825



Ex-vivo release kinetics of (F_{10}) in simulated salivary fluid.

Conclusion: The oral disintegrating tablet formulations of Valsartan were prepared by direct compression technique using superdisintegrant crospovidone & Indion 204 as taste masking agent in different concenterations. A total of 10 batches were prepared.

The characteristic IR peaks of the pure drug were compared with that obtained with drug and polymer mixture which remained nearly same and the thin layer chromatographs of the pure drug & that obtained with different formulation blends of various batches confirmed approximately equivalent R_f values. Conclusively Valsartan was found to be compatible with the ingredients incorporated in oral disintegrating tablet formulations.

Various physicochemical parameters determined with the bulk material were angle of repose (31-34), bulk density (0.41-0.43), tapped density (0.47-0.49) and compressibility index (11-14%).

The prepared tablets were also evaluated for various post-compression parameters and results depicted weight variation (185-195), friability (0.04-0.40), hardness (1.6-2.3), in-vitro disintegration time (20-72 sec) and percent drug content(98-101%).

In-vitro release of the drug from the optimized batch (F10) in pH 6.8 phosphate buffer solution was 97.42% & in simulated

salivary fluid it was 96.81%. All above data satisfactorily complied with the characteristic requirements of the formulation of oral disintegrating tablet.

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