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Formulation and *in Vitro* Evaluation of Valsartan Flash Tablet

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ABSTRACT

Introduction: Flash tablet is one of the newer technologies that recently have been focused on. flash tablet offers many advantages such as fast disintegration and dissolution. However, it has many issues and drawbacks such as fragility of the final tablet and difficult manufacturing process. In this work valsartan (the antihypertensive medication) was fabricated as lyophilized tablets to improve its dissolution profile and bring about all the advantages of this drug delivery system, such as rapid disintegration.
Materials and Methods: Mannitol, hydroxylpropyl methyl cellulose (HPMC 5E) and tween 80 were used as matrix, binder, and dissolution enhancer; respectively. The effect of their concentrations on physiochemical properties were evaluated *in vitro* by conducting mechanical strength test, content uniformity, weight variation test, and the dissolution profile.
Results: The hardness and friability have shown using HPMC 5E at concentration 5% will yield a better mechanical property and the best disintegration time. Dissolution profile have shown that using tween 80 at concentration 1% would improve valsartan dissolution significantly.
Conclusion: Valsartan flash tablet offers a good alternative to plain tablet with acceptable pharmaceutical properties.

Keywords: Flash tablet, orally disintegrated tablet, valsartan, dissolution profile

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INTRODUCTION

One of recent advanced dosage forms is fast dissolved oral tablets (FDTs) or flash tablet which releases the drug inside the mouth within very short time [1]. FDTs have the ability to dissolve in saliva or disperse in mouth within seconds; hence provide fast releasing rate mainly for water insoluble medicines. The released active moiety, thereafter, absorbed through the pharynx or esophagus. Therefore, the bioavailability of such poorly absorbed drug will increase significantly [2]. FDTs also provide protection from first pass metabolism. Furthermore they could be given to comatose patients and children and those people who cannot swallow [3]. Flash tablets could be crafted by many techniques; such as lyophilisation, molding, spray drying, mass extrusion and compaction [4]. Although freeze drying preparation method is considered as an expensive method of preparation, Lyophilized tablet can deliver the very poorly water-soluble drug within less than 5 second. This represents a quite strong reason why this technique is still an attractive method for manufacturing of fast dissolving tablets [2]. Valsartan is one of angiotensin II receptor blockers. The fraction of absorbed valsartan is circa 10-35% [5, 6]. It is classified as class III drug according to biopharmaceutical classification scheme; with poor permeability and high solubility [7, 8].

C.P. Jain and P.S. Nnaruka has developed a fast dissolving tablets for valsartan by direct compression using super disintegrates (Crospovidone, Ac-Di-Sol, Sodium Starch Glycolate and Microcrystalline cellulose). Unfortunately, they had to use at least two disintegrants in each formula to achieve the required disintegration [9]. Ibrahim and El-Setouhy had tested the usage of several binders (e.g., gelatin and pectin) and matrices (e.g., mannitol) for valsartan oral dispersible tablets without the use of any solubility enhancing agents [10]. In more recent study, Hussainy R A *et al* prepared 40 mg of fast dissolving tablet of valsartan. Although they had used different types of super disintigrants with different binders, all formulas required more than 15 min to release 80% of the drug [11].

Mbah C had shown that the use of 1% of tween 80 led to increase valsartan aqueous solubility by 20 times [12]. Such solubility enhancement might improve valsartan bioavailability by increasing its dissolution. During this work, minimum numbers of the required excipients was used to yield an acceptable flash tablet dosage form. The effect of binder concentration (HPMC 5E) and solubilizing agent (tween 80) was examined to achieve flash lyophilized tablet with best mechanical properties and dissolution profile; hence provide better absorption. Valsartan dose was selected to be 40 mg the minim dose available in the market. The valsartan was incorporate with mannitol by freeze drying technique as filler. HPMC 5E was add as binder and the effect of its concentration variation was investigated.

MATERIALS AND METHODS

Materials

All materials were of analytical grade with 99% quality unless indicated otherwise. Valsartan, mannitol, sodium saccharine were a gift form Samalfayha drug industry; Basrah; IRAQ. hydorxypropyl methylcellulose (HPMC 5E) (LAB Chem Fine Chemicals Mumbai; INDIA), Tween 80 (LAB Chem Fine Chemicals Mumbai; INDIA).

Standard calibration curve and lambda max (λ)

The lambda max was determined by scanning several concentrations in 200-400 nm. An accurately weight of valsartan was dissolved in specific volume of phosphate buffer (pH=6.6) to get a stock solution with concentration of 1000 µg/ml. Calibration curve was plotted by measuring the absorbance of several aliquots 10, 20, 30, 40, 50, 60, 70, 80, 90, 100 µg of valsartan in buffer system pH=6.6 at lambda max [13].

Preparation of the lyophilized tablets of valsartan

For each batch, 30 tablets were prepared by lyophilisation method reported by Corveleyn S *et al* [14]. The component of each tablet of each batch is stated in Table 1. HPMC 5E, sodium saccharine, tween 80, and

mannitol was dissolved in 20 ml of water consequently using magnetic stirrer. The required amount of valsartan was dispersed in the resultant solution; and the volume was completed up to 30 ml. One ml of final dispersion was transferred into 1 ml capacity PVC empty blister to be frozen overnight at -5 ºC. Then lyophilized for 24 hrs using Labconco freeze dryer, USA. The resultant tablets were kept in desiccator to prevent moisture absorption for evaluation. In the flash tablet preparation, the percentage of mannitol was fixed to omit the effect of filler ratio on tablet disintegration and improve the sensitivity of the test in detecting the changes due to variables under investigation.

Table 1: The formulation code and amount of each component required to prepare one tablet.

FORMULA CODE	*Valsartan (mg)*	*Mannitol (mg)*	*HPMC 5E% w/w*	*Tween 80% of W/V*	*Sodium saccharine (mg)*	*theoretical total weight (mg) of each tablet*
F1	40	260	0	0	2.5	302.5
F2	40	260	0	1	2.5	305.5
F3	40	260	0	2	2.5	308.5
F4	40	260	0	3	2.5	311.5
F5	40	260	2	0	2.5	308.5
F6	40	260	2	1	2.5	311.5
F7	40	260	2	2	2.5	314.5
F8	40	260	2	3	2.5	317.5
F9	40	260	5	0	2.5	317.5
F10	40	260	5	1	2.5	320.5
F11	40	260	5	2	2.5	323.5
F12	40	260	5	3	2.5	326.5
F13	40	260	10	0	2.5	332.5
F14	40	260	10	1	2.5	335.5
F15	40	260	10	2	2.5	338.5
F16	40	260	10	3	2.5	341.5

Evaluation of Tablets (General appearance, Weight variation test, mechanical strength, Wetting time, Water absorption ratio, and In vitro disintegration test)

The general appearance for 30 tablets was inspected for fissuring and cracking. The general quality tests are conducted according to USP. For weight variation test, the weights of 20 tablets were measured individually and the mean weight was reported with its standard deviation[15]. The hardness of three tablets from each batch was measured by using hardness tester (ERWEKA, GERMANY). The maximum load that each tablet can handle before any crack appears was recorded in Kg. For friability test, 20 tablets were placed in friability tester (Erweka; Germany). The weight before and after performing 100 revolutions in fraibilator was recorded to measure the friability percentage. The disintegration test was performed on six tablets using pharma test disintegration tester (Pharmatest; Germany), the media for disintegration was distilled water at 37°C±1°C according to USP [15, 16]. The wetting time was recorded by placing five circular filter paper 10 cm in diameter in a 10 cm diameter Petri dish. This Petri dish was filled with 10 ml of distilled water that coloured by water soluble food colouring agent. After placing the tablet on the wetted paper, the time (in seconds) was recorded for the coloured water to reach the top surface of tablet. The wetting test represents the average of three measurements [17, 18]. Water absorption was measured simultaneously with measuring the wetting time by recording the weight before and after wetting. The water absorption ratio was expressed as average of three measurement using the following equation [17]:

Water absorption ratio= 100(weight after absorption- initial weight)/initial weight

Content Uniformity Test

The content uniformity was assayed by grinding 10 tablets. Then, an equivalent weight of the powder containing 10 mg of valsartan was transferred into 100 ml volumetric flask and dissolved in 100 ml phosphate buffer pH=6.6 and sonicated for 5 minutes. The solution was filtered and diluted 10 times. The absorbance was measured at λ=250 nm Using Cecil spectrophotometer [9].

In Vitro Dissolution Profile

Cumulative drug release profile was performed to the plain drug, brand tablet and the successful formula from physical tests. Five unite dosage of each examined sample was subjected to dissolution test and the results were expressed as average of three (n=5) according to USP. The test was performed with basket type dissolution tester (apparatus II), at 50 rpm speed, in 500 ml phosphate buffer (pH=6.6) at 37 ± 0.5°C. A sample of 3 ml was collected each 2 minutes and replaced with fresh media and the test was run for 45 minutes. For dissolution test, Caleva 11ST dissolution tester; Germany was used. The absorbance was measured by using Cecil spectrophotometer at λ=250 nm against blank solution.

The retained concentration was then calculated form the prepared calibration curve [10, 15, 19].

Kinetics of Drug Release Profile

The cumulative amount of valsartan release from flash tablets at different time intervals was fitted to zero order kinetics, and first order kinetics, to characterize mechanism of drug release[20].

Zero Order Kinetic

When the drug release from pharmaceutical dosage forms is independent on concentration, the system follows zero order kinetics:

$$A_t = A_o + K_o t$$

A_0 is usually equal to zero and it represents the initial part of the drug that dissolved in the dissolution medium, whereas A_t is amount of drug dissolved in time t. K_0 is the zero order constant of the dissolution process. When the plot of at against t gives straight line, the system will follow zero order kinetic with slope equal to K_0 and intercept of A_0 (i.e. zero).

First Order Kinetic

When the drug release from pharmaceutical dosage forms is dependent on concentration, the system follows first order kinetics:

$$log\ at = log\ A_o + k_1\ t\ /\ 2.303$$

Where A_t is the amount of drug dissoluted after t time. A_0 is the initial amount of drug in the dissolution medium and K_1 is the first order constant of the dissolution process. If the plot of log (A_0- A_t) versus t is a straight line, the first order drug release kinetic is obeyed with a slope of (K_1 / 2.303) and an intercept at t = 0 of log A_0.

Statistical Study

All tests were performed as triplicate unless otherwise stated. The results of the experiments are given as a mean of triplicate samples ± standard deviation. To determine significant difference, the one-way analysis of variance (ANOVA) at the level of ($P < 0.05$) was used. The dissolution profile comparison was made by model independent method (similarity *(f1)* and difference *(f2)* factors) and DD solver add in package was used for calculations [21].

RESULTS AND DISSCUTTIONS

Calibration Curve:

The calibration curve of valsartan in phosphate buffer pH=6.6 was plotted by measuring the absorbance of 10 concentrations range from 10 µg to 100 µg/ml at λ max=250nm. The linear range (Figure 1) obeys Beers-Lambert law was from 10 – 60 µg/ml with R^2 of 0.9985. Linear equation was found to be (y = 0.019x - 0.029). The molar absorptivity coefficient of valsartan at 250 nm was $8.2*10^4$ L/(cm.mol). The limit of detection and limit of quantification were 2.1 µg/ml and 6.3 µg/ml; respectively [22].

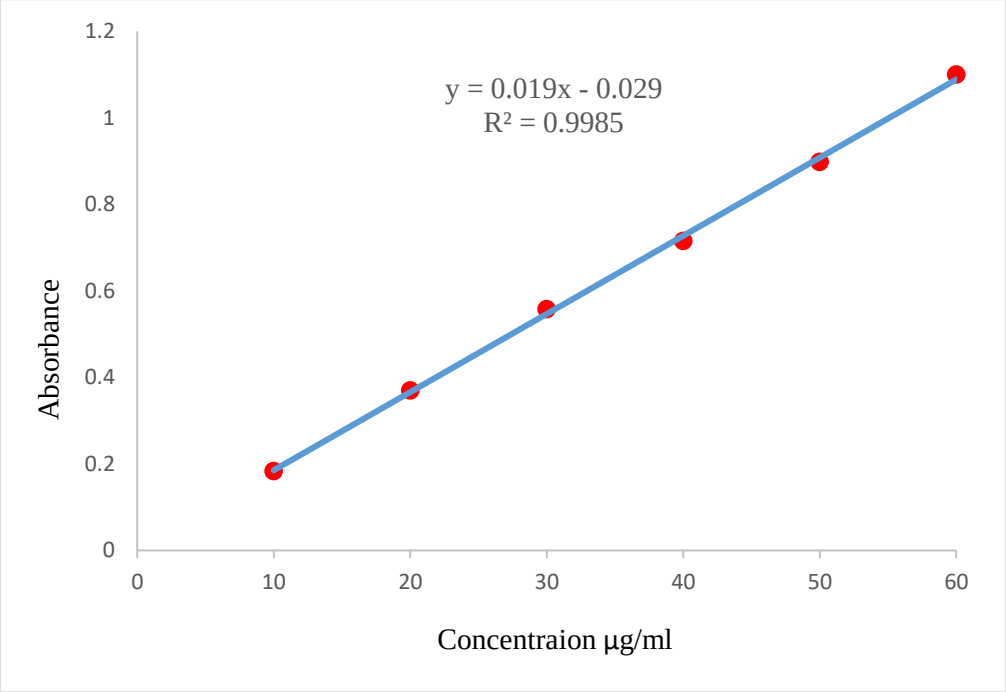

Figure 1: calibration curve of valsartan in phosphate buffer pH=6.6 at lambda max=250 nm

Physical Characterization of Valsartan Flash Tablet

A summary of physical parameters of valsartan flash tablet is listed in Table 2. All the prepared tablets were accepted in shape. They had elegant rough surface, except formulations (F1-F4). F1-F4 resulted in broken friable tablets and they were difficult to remove form blisters. This defect could be as result from lacking binder (HPMC 5E% = 0) in these formulations. Thus, F1-F4 were excluded from further testing. The hardness testing of formulations having concentration of binder of 2% revealed that those formulations (F5 to F8) were soft tablets. One-way ANOVA for comparison of the tablet hardness was conducted to the formulas F5 to F16. The statistical results showed that the formulations having higher concentrations of HPMC 5E, 5% and 10%, had shown significant change ($p < 0.05$) in hardness in comparison to those having 2% (Table 2). However, there was no significant difference ($p > 0.05$) in hardness between 5% and 10% binder concentration as shown in Table 2. Formulations containing 2% of binder (F5-F8) had shown unacceptable friability results (>1%). Therefore, F5-F8 were excluded form dissolution study.

In comparison, formulations containing binder concentration more than 2 % (i.e., 5% and 10%, F9-F16) have shown acceptable margin of friability (<1%) as demonstrated in Table 2 [15]. Therefore, adding HPMC 5E at concentration not more than 5% of total formulation could be recommended. The results were in accordance with Ahmed *et al* [23], who prepared nimesulide lyophilized tablet with increasing concentrations of HPMC 5E as binder. Ahmed *et al* found that the use of HPMC 5E in concentration of 2% resulted in more friable and less hard tablet and they suggest the use of HPMC 5E in higher concentrations. The use of low concentration of HPMC 5E (that might not be enough to bind the tablet solid components) is the reason for such reduction in mechanical properties of valsartan flash tablet.

Table 1: Pharmaceutical properties of the prepared flash tablets

FORMULA	*hardness (KG)*	*friability (1%)*	*wetting time (sec.)*	*water absorption ratio*	*Disintegration time (sec)*	*Average weight (mg)*	*Content uniformity (mg)*
F1	-	-	-	-	-	-	-
F2	-	-	-	-	-	-	-
F3	-	-	-	-	-	-	-
F4	-	-	-	-	-	-	-
F5	0.2 ± 0.1	3.00%	38 ± 3	152 ± 2	8 ± 3.6	318 ± 3	38.5 ± 1.46
F6	0.1 ± 0.11	2.00%	36 ± 3	149 ± 4	9 ± 1.5	321 ± 3	38.2 ± 1.76
F7	0.3 ± 0.25	3.50%	39 ± 3	148 ± 2	16 ± 2.1	323 ± 2	41.4 ± 1.42
F8	0.11 ± 0.26	1.40%	42 ± 4	146 ± 3	14 ± 2.6	325 ± 2	38.9 ± 1.53
F9	0.6 ± 0.1	0.00%	35 ± 3	145 ± 4	12 ± 2.1	327 ± 3	41.7 ± 1.48
F10	0.5 ± 0.13	0.10%	42 ± 3	142 ± 3	13 ± 2.1	330 ± 3	42 ± 1.88
F11	0.4 ± 0.18	0.00%	36 ± 11	140 ± 9	15 ± 3.2	334 ± 5	42.1 ± 1.58
F12	0.65 ± 0.1	0.30%	38 ± 9	137 ± 7	15 ± 2.9	338 ± 5	39 ± 0.96
F13	0.75 ± 0.11	0.10%	43 ± 8	134 ± 5	28 ± 2.5	342 ± 3	38.6 ± 0.96
F14	0.56 ± 0.03	0.50%	60 ± 12	132 ± 10	24 ± 3.1	345 ± 3	39.5 ± 0.66
F15	0.55 ± 0.04	0.10%	45 ± 9	131 ± 5	22 ± 2.8	347 ± 2	40.8 ± 0.35
F16	0.6±0.03	0.60%	55 ± 8	139 ± 4	34 ± 3.1	335 ± 4	40.3 ± 1.47

The wetting time for HPMC 5E concentration 2% and 5% ranges from 35-42 seconds. Whereas the wetting time for 10% HPMC 5E ranges form 43-60 seconds. The high concentration of binder might retard the water absorption. The absorption ratio revealed very good absorption capacity for all formulation, and no one has a superior absorption power over the other ($p > 0.05$). This could be as a result of high porosity of the resultant tablets as it was prepared by freeze drying technology. The correlation between wetting and flash tablet disintegration have been studied previously by He *et al* [24]. They found that the presence of high concentration of HPMC might affect the integrity of the porosity of the lyophilized tablet and subsequently affecting the tablet wetting and disintegration.

All batches disintegrate within seconds, (8-34 seconds). Thus all tablets had accepted disintegration profile and meet the disintegration criterion for lyophilized tablet [3]. However, the concentration of HPMC 5E has significant effect on disintegration time ($p < 0.05$). The disintegration time is affected negatively at 10% concentration of HPMC 5E in formulation. Formula F13-F16 have shown disintegration time up to 34 seconds. Therefore, the binder should not exceed 5% of total formulation. These findings are in accordance with results from wetting time (Table 2); Formulas F13-F16 have shown longest wetting time. Therefore, F13-F16 were excluded form dissolution profile study. Similar results have been noticed by Al-Amodi *et al* [25]. They found that the retardant in disintegration due to the use of high concentration of HPMC is attributed to the ability of HPMC to form cross-linking network that block the pores within the tablet and improve its hardness. The results of weight variation test and content uniformity suggested uniform distribution of dispersed solid material in suspension. The relative standard deviation values of all formulation are less than ±5% for both content uniformity and weight variation tests. That might be result from using highly concentration dispersion system and presence of binder which produce stable dispersion. Similar results had been reported by El-Nabarawi *et al* for diclofenac flash tablet [26].

Dissolution Study

The dissolution profile (Figure 2) was performed for formulations F9-F12 to study the effect of lypohilzation and the effect of concentration of the solubilizing agent (tween 80) on dissolution profile.

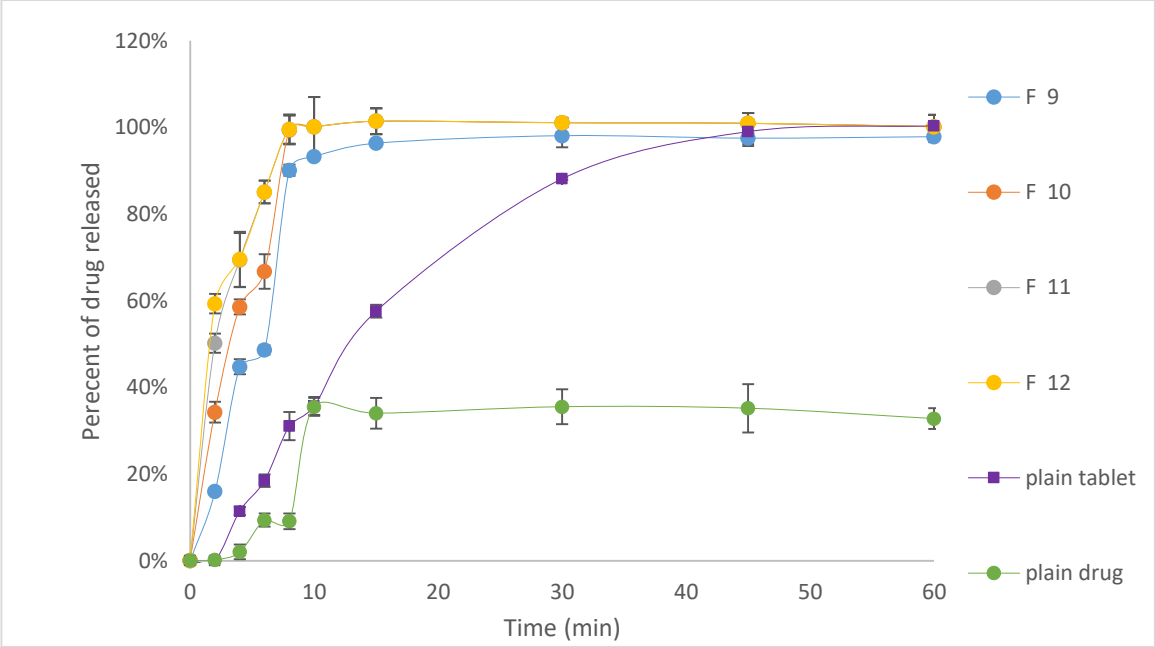

Figure 2: the dissolution profile at the candidate formulations (F9, F10, F11, F12), plain drug, and plain tablet in phosphate buffer pH=6.6.

More than 80 % of drug content of F11, and F12 has released within 6 minutes. Whereas 62% of drug in formulation F11 has released within first six minutes. In contrast, formulation containing nil surfactant has released 47% of its drug content after 6 minutes. Thus, the dissolution is significantly affected by presence of tween 80. In similar pattern, Chakma S *et al* indicated that tween 80 can improve the solubility and dissolution of celecoxib compare to ordinary tablet [27]. The comparison of significant differences among dissolution profiles is demonstrated in Table 3. The similarity factor (*f1*) and difference factor (*f2*) have been used as independent variable analysis of dissolution profile.

Table 3: Similarity and difference factors of flash and plain tablets of valsartan

	Plain drug/F9	***Tab/F9***	***F9/F10***	***F10/F11***	***F11/F12***
Similarity factor (f1)	**80.71**	**66.87**	**22.67**	**12.58**	**2.29**
Difference factor (f2)	**16.18**	**20.51**	**44.53**	**48.14**	**70.72**
Similarity factor =50-100 similar *Difference factor =1-15 similar*					

Form Table 3, the dissolution profile of formulation F10, F11 and F12 are similar because they all have acceptable similarity and difference factors among each other. However, they differ from F9 dissolution profile which is clearly shown that adding tween 80 had significant effect on dissolution profile of the lyophilized tablet of valsartan. On the other hand, in this study, the addition of the surfactant agent at concentration more than 1% (i.e. 2% or 3%) would not improve the dissolution profile.

Dissolution Kinetics:

The release kinetics of valsartan from the selected flash tablets was determined by finding the best fitting of the dissolution data to the mathematical models is demonstrated in Table 4.

Table 4: Valsartan release kinetics from prepared formulas

Formula No	**Kinetic Model**			
	Zero order		**First order**	
	K_0 mg.min^{-1}	**R^2**	**K_1 min^{-1}**	**R^2**
F9	8.719	0.9143	0.1208	**0.9307**
F10	11.218	0.9364	0.1883	**0.9807**
F11	13.709	0.9184	0.3099	**0.9948**
F12	13.261	0.8947	0.3001	**0.9667**
Plain tablet	4.065	**0.9828**	0.0736	0.9611
Plain drug	2.712	**0.8027**	0.0173	0.6541

Formulas F9 to F12 exhibit a good fitness to first order model (best results in **bold**), while plain tablet and drug better fitted to zero-order model. The results were in accordance with Mulye and Turco, who suggested that first order kinetics is associated with a release of drug from a porous dosage form (such as valsartan lyophilized tablet). Additionally, after fast disintegration the dissolution behavior will be derived mainly by Noyes-Whitney rule of dissolution of solid particles that's mainly depend on concentration gradient [28].

CONCLUSIONS

Valsartan lyophilized tablet could offer a good alternative to plain tablet for those patients who suffering from swallowing difficulties or those patients who cannot get hold of water to swallow the ordinary tablet. In light of this work, the formulated valsartan lyophilized tablet can be manufactured with satisfactory properties (i.e., pharmaceutical properties) from mannitol as filler, HPMC 5E as binder, and tween 80 to enhance dissolution profile. It showed better dissolution profile in comparison with the plain tablet. In this study binder formula containing binder at concentration 5% and surfactant 1% would be suggested as the best formula. This study represents *in vitro* evaluation which enlighten the *in vivo* study and pave the way for testing it on animal or human volunteers. Also, long stability study is necessary to assay the long-term stability. Furthermore, studying the polymorphic changes by other methods such as differential scanning calorimetry might be needed.

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