Research Article

Formulation And Development Of Valsartan As An Oral Dosage Form (Capsule)

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Abstract

The objectives of this study were to develop the formulation of valsartan to improve dissolution profile using central composite design. Valsartan is a anti-hypertensive oral dosage form used for treatment hypertension and myocardial infraction it is poorly soluble drug with low dissolution rate. In this study 20 different formulations of valsartan were prepared by varied amount of PEG-600, PG, and PEG-400, with other excipients as per the central composite design protocol. Central composite design was used to choose the optimize condition with improved dissolution profile. The optimum formulation was F-5 which was containing PEG-400, PG and PEG-600 in a ratio of 25:25:60. The physical properties of different formulations like uniformity, the angle of repose, Carr's Index, weight variation, appearance and drug release were in the acceptable range.

The rate of release valsartan from formulation F-5 was more than 72% after 2 hours, while the formulation F-7 showed only 35% of drug release. Formulation F-5 was further improved by the addition of $KHCO_3$ (2.5 w/w %), which release 86% valsartan in-comparison to marketed formulation Diovan (96%). Fourier transforms infrared spectroscopy (FT-IR) and HPLC indicate that there were no interaction between the valsartan and the excipients used. No adduct formation or degraded products were observed using HPLC. The stability studies were carried out as per the ICH guidelines. The formulations were stable during the study period. Finally it can be concluded that developed formulation of valsartan is stable and can be further improved for routine purpose on the basis of current data.

1. Introduction

There are numerous sparingly soluble active pharmaceutical ingredients whose formulation presents greater challenges for a formulation due to its poor dissolution characteristics. For insoluble or poorly soluble drugs, the rate of oral absorption and extent of bioavailability is often controlled by the dissolution rate in the gastrointestinal tract. The solubility, permeability and dissolution behavior of a drug are key determinants of its oral bioavailability. Therefore the need is to improve the drug dissolution rate which can increase the therapeutic efficacy and also maintain the effect over a desired period of time. Since there is increasing cost and complications involved in development and marketing of new drug entities, this has forced industries to focus their attention on the development of solid dispersion systems. In vitro biopharmaceutical studies are designed to overcome both the solubility and permeability characteristic of a poorly soluble drug (Nahar and Jain, 2006).

Valsartan is a potent, extremely non peptide selective powerful chemical, belongs to a class of medications called angiotensin receptor blocker (ARB) selective for type AT1 subtype. Valsartan drug is used orally to treat a variety of cardiac conditions including high pressure and congestive heart failure, due to its vaso-dilation powerful effect. The trial incontestable of valsartan in heart diseases approved its efficiency in reducing rates of heart failure related hospitalizations and shorter mortality length (Jain et al. 2010). Valsartan is poor water-soluble drug (BCS-Class-II) with, high permeability, low solubility and poor metabolism according to Biopharmaceutics Classification System (BCS) and bio-pharmaceutics drug disposition classification system (BDDCS). BDDCS is a guide for predicting the intestinal drug absorption provided by the U.S. Food and Drug Administration. Several studies and reports had been recorded to evaluate and measure the variation of valsartan bioavailability in order to enhance its solubility in the formulation of oral dosage form (Smith et al., 2005).

Valsartan is developed by Novartis Company and marketed as "DIOVAN" and holds the largest market share for the drug of its kind in the market worldwide. Valsartan is approved by US-FDA, since 2008, as hypertension therapy for children above 6 years and adolescents (Siddiqui et al., 2011).

1.2 Physicochemical Properties

Valsartan has a chemical formula of C24H29N5O3 and a relative molecular mass of 435.5 g/mol. It is (2S)-three-methyl-2-[pentanoyl-[[4-[2-(2H-tetrazol-5-yl) phenyl] phenyl] methyl] amino] butanoic acid (Fig. 1) Valsartan is white crystalline powder with melting point ranging between 116-117 °C, synthesized in 1990. The 10 steps of synthesis process of valsartan started from L-valine methyl group ester hydrochloride yielded 60 % of the material in the fourth step. In addition they found that valsartan is S-enantiomer [partition coefficient is 0.033 (log P = 1.499)], suggesting that the compound is hydrophilic at physiological pH (Saydam and |Takka, 2007)

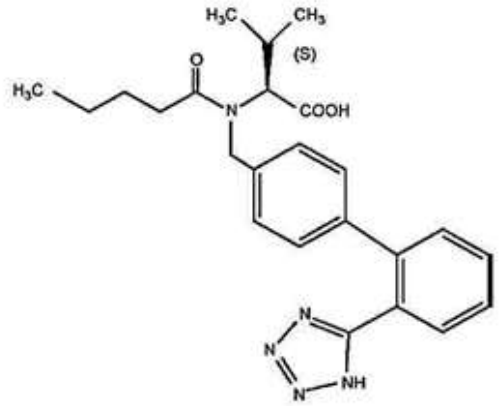

Figure 1.1: Chemical structure of valsartan.

Valsartan adsorbs water reversibly from ambient atmosphere due to its fine particle size. The preparation of aqueous solution in buffers of pH of 6 produces stable aqueous solution because plays a crucial role in ionizable molecules (Saydam and Takka, 2007). The ionization constant (pKa) of a molecule at a particular pH dictates the charge state of that molecule. pH gradients in the unstirred water layers can be affected by using buffers, which change the dissolution and permeability of ionizable molecules (Avdeef, 2001).Weakly basic drug, weakly acidic drug and salts affect the demonstration of pH-dependent solubility form. For example, in weak acids, the contribution of the ionized form; increases the solubility of acid due to pH value rise. The two weakly acidic functional groups of valsartan have pKa values of 3.9 and 4.7 (Hörter and Dressman, 2001). Valsartan can coexists as the mono-anion and di-anion. At physiological pH, and high pH value from 4 to 6 enhances the solubility of valsartan by a factor of about 1000 and decreases the lipophilicity. At pH 5.0 and above, In vitro, the dissolution of this compound is rapid and complete while the solubility is limited at pH 3.0 and below. Its observed That intestinal pH (5-8) has a great effect on the rate of absorption of valsartan where the solubility increases and lipophilicity decreases.(Amidon, et al., 1995; Wu and Benet, 2005).

The solubility of valsartan in water at 25°C is approximately 0.18 g/L. and in case the phosphate buffered solution (pH 8.0), the di-anion salt is formed and that increase the solubility. Valsartan is soluble at pH (8.0) to the extent of 16.8 g/L, yielding a pH of 5.29 for the saturated solution (Saydam and Takka, 2007).

1.3 Importance of Solubility and Dissolution in Drug Formulation

The proper dissolution and solubility of active pharmaceutical ingredients in the pharmaceutical formulations presents grate challenges for the formulators, whose responsible for present a potent therapeutic medication with recommended bioavailability. The rate of oral absorption and extent of bioavailability are controlled by the solubility and dissolution rate in the gastrointestinal tract.

The solubility, permeability and dissolution behaviors of a drug are key determinants of its oral bioavailability. Therefore, it is very important to improve the drug solubility and dissolution rate in order to increase the therapeutic efficacy and maintain the effect over a desired period of time (Gibson, 2016).

The solubility of drug molecules affects the bioavailability and therapeutic efficacy. Recently, only 8 % of new medications have good permeability and solubility (Liu, R., 2008; Savjani,et al.2012).

The principle project of any drug formulation development is to achieve the selective medication with maximum therapeutic efficacy and lower dose special techniques are required to increase the solubility of poorly water-soluble drugs, such as pH adjustment, particle size reduction, solid dispersions and inclusion complex formation.(Brahmankar, and Jaiswal, 2009).

Valsartan is classified as poorly soluble drug, the solubility of drug in water was less than one mg/ml (Cappello, et al. 2006). According to the AUC values obtained, the bioavailability of capsule was 23% and that of solution was 39%. (Saydam and Takka 2007). Generally, compounds with liquid solubility lower than100 mg/mL show dissolution-limited absorption (Hörter and Dressman, 2001) or Erratic and/or incomplete absorption from the GI tract of animals and humans (Wong et al 2006.)

Micronization and nanosuspension techniques are used to reduce particle size of the molecules that modifies the crystal habit like polymorphs, amorphous type. Co-crystallization, drug dispersion in carriers like, solid dispersions, eutectic mixtures, solid solutions and refrigerant techniques have also used in particle size reduction (Kumar et al. 2013).

The solubility of the poorly soluble drugs can be increased by chemical changes like change of pH scale, use of buffer, derivatization, complexation, and salt formation. Other methods like supercritical fluid method, use of adjuvant like chemical agent, solubilizes co-solvency, hydrotrophy, and novel excipients are also applied to improve the solubility characteristics (Savjani et al., 2012).

2. Materials

Valsartan (99.5%) was obtained as a gift sample from United Pharmaceutical Manufacturing Company, Amman, Jordan. Polyethylene glycol 400 (PEG 400), polyethylene glycol 600 (PEG 600); polyvinylpyrrolidone (PVP), Potassium phosphate mono-basic (KH_2PO_4), propylene glycol (PG), sodium lauryl sulfate (SLS) were procured from Sigma-Aldrich, USA. microcrystalline cellulose (MCC), lactose and Tween-20 were procured from JRS Pharma, Germany, Alpha Chemika, India and Lab-Chem, USA, respectively. Analytical grade solvents were purchased from Fisher Scientific, UK and used as such.

2.2 Instrumentation

Shimadzu Prominence Liquid Chromatograph consists of reciprocating quaternary gradient Pump (Shimadzu-20-AD UFLC, Degasser– DGU-20A_3 Prominence Degasser), Auto-sampler and injector (SIL-20A Prominence auto-sampler), Detector (photo diode Array detector, SPD-M20A), Communication Bus module (CBM-20A) and C-18 column (Hypersil-Gold, C-18, 100 mm x 4.6 mm, Particle size- 5 µm, Thermo-Fisher, USA) was used. Single Pan Digital Balance (Shimadzu Model-AUX-220, Japan) and Ultra-violet (UV) spectrophotometer (V-530, version. 1.50.00, JASCO, Japan) controlled by Windows NT based Spectra manager were used. Melting point apparatus (Electro thermal 9100, Mettler DL67 titrator 0.18µA, UK) for recording melting points and INOLAB pH meter (model 720-WTW, Weilheim, Germany) for measuring pH were also used. Fourier transform Infra-red (FTIR) spectrophotometer (IR Prestige-21, Shimadzu, USA) and a UV-Visible spectrophotometer (UV-1800, Shimadzu, Japan) were utilized. Polarimeter (Polax-2L, Atago, Japan) was used for determination of specific rotation. Erweka dissolution test instrument (Ottostraße, Germany); humidity controlled Oven (Memmert, Germany), Vortex mixer (VELP Scientifica, Europe), Vacuum Filtration unit, ultrasonic bath (Bronson), water bath (Buci, Switzerland), Magnetic stirrer and centrifuge were used.

2.3 Glass-wares

Glass wares such as volumetric flasks (Isolab, Germany, Class A, DIN), pipettes (Isolab, Germany Class 2Aa, DIN), and other glass-wares were used for the experimental purpose. Micro-pipettes (Socorex, ISBA S.A., Switzerland) of 100µl and 1000µl capacity were used.

2.4 Pre-formulation Studies

This is a stage of the study during which some physicochemical properties of drug substance are characterized. This stage is important to develop the final formulation with higher quality, lower expenses and shorter duration since that the information gained at this step will support many subsequent events and approaches in the formulation process. The studied parameters include drug identification by different devices, melting points determination, water content, and interaction studies using FT-IR and HPLC.

2.4.1 Melting Point Determination

The melting point of the valsartan was determined by using Electrothermal (Cat. No. AZ 9003-60w) melting point apparatus. The melting points were determined in capillary tubes and are uncorrected.

2.4.2 Water Content (Karl Fischer Method)

Water content in the drugs was determined by using Mettler DL67 titrator 0.18 µA. The method involved the standardization of Karl Fischer reagent using Sodium tartrate dehydrate using methanol as a solvent. Later on, percent moisture content of valsartan was determined using standard procedure (Beckett and Stanlake, 1988).

2.4.3 Specific Rotation

Valsartan (0.25g) was accurately weighed and transferred to a 25 ml volumetric flask. It was dissolved in small quantity of methanol and then volume was made up to 25 ml. Zero adjustment of the polarimeter was carried out using methanol using 2 dm cell. Then the observed rotation of the valsartan solution was determined and the specific rotation was calculated using the given formula.

2.4.4 Ultra-violet (UV) Spectroscopy

The λ_{max} of valsartan was determined in different mediums like methanol, phosphate buffer solution (pH 6.8), using UV spectrophotometer (Shimadzu, UV-1800) in the range of 200-350 nm. The phosphate buffer solution (pH 6.8) was prepared using Potassium phosphate buffer concentrate pH 6.8 (Sigma-Aldrich, USA). The working solutions were scanned (λ 200-350nm) and the λ_{max} for the valsartan was determined.

2.4.5 Infrared spectroscopic analysis of drug

IR spectra of valsartan, PVP, SLS, lactose, and formulation were recorded with KBr disk method using Fourier transform infra-red absorption spectrometer (IRPrestige-21, Shimadzu, Japan) alone or in combination with API (valsartan) to study compatibility of excipients. Approximately 1-2 % mixture of each solid sample in KBr (anhydrous) was triturated using agate pestle-mortar and discs were prepared using hydraulic press. The IR spectra were recorded between 4000-400 cm^{-1}. The resultant data were then collected for interpretation. Spectrophotometer grade potassium bromide is extremely hygroscopic, that is why it was essential to dry it for about 4 hours at 110° C and then store it in desiccators to eliminate moisture (Griffiths and De Haseth, 2007). The IR spectroscopy is also used for the identification of drug.

2.5 Drug-excpients Interaction

While designing any new drug delivery system, it is of great importance to detect whether or not the active ingredients are compatible with each other and with the excipients. Many methods are known to determine such interactions, therefore, within this study the Infrared spectroscopy and HPLC were used.

2.6 Drug Content Evaluation by HPLC

This is an important analytical tool in the separation and identification of different drugs depending on the difference in the migration of solutes between two phases; stationary and mobile phases. This migration occurs as a result of the adsorption of substances on the stationary phase that acts as an adsorbent. The HPLC analysis using photo diode array detector (PDA) was conducted for known amount of valsartan with different excipients. The peak purity index and UV spectra was checked for valsartan and other signals. The peak purity index of more than 0.98 indicates the absence of any co-eluting signal with valsartan. Also the drug content of the valsartan and presence or absence of secondary signals was recorded. Drug content close to true value indicates no incompatibility. Also by comparing the retention time of the drug alone and in combinations, it was possible to identify whether or not an interaction between different components had occurred.

For chromatographic analysis, Shimadzu® HPLC equipped with quaternary gradient pump (LC-20AT) was used. The signals were acquired and analyzed using LC Solution version 1.25, Shimadzu corporation software. The separation of the compounds was made on a ODS-C_{18}-Hypercil GOLD column (150mm × 4.6mm) at 25±2 °C temperature. The mobile phase was water (containing 0.25 ml/L triethylamine), methanol and acetonitrile (50/38/37, v/v/v). The final pH of mobile phase was adjusted to 3.0±0.1 with orthophosphoric acid (OPA). Mobile phase was filtered through 0.45µm nylon filters (Millipore, USA) and degassed in an ultrasonic bath before use. All analyses were performed under isocratic condition. The injection volume was 10 µl. The peak areas and retention time of valsartan was recorded. Calibration curves were prepared using working solution and the concentrations of the samples were calculated using the appropriate curves. The mobile phase flow rate was 1.0 ml /min., in all the analysis (Shakya, AK, 2016).

2.9.7 Stability Studies

A stability study was performed to determine the effect of temperature and humidity with time on the drugs` content in the prepared formulation. A drug formulation is said to be stable if it fulfills the following requirements.

- It should contain at least 90 % of the stated active ingredient.

- It should contain effective concentration of added preservatives, if any
- It should neither exhibit discoloration or precipitation, nor develops foul odor.
- It should not develop irritation or toxicity.

Capsules (10 caps each of optimized formulation) were collected randomly from the lot placed in glass tubes and stoppered. These tubes were stored at 25°C (60% RH), 30°C (75% RH) and 40°C (75% RH) as per ICH guideline. These capsules were evaluated at 0, 30 and 90 days for the drug content and organoleptic evaluation. The shelf life was determined using standard procedure.

Table 3-1a: Designed Formulation (F1-F8) using central composite design, respective constituents and quantity

Ingredients* (mg)	F1	F2	F3	F4	F5	F6	F7	F8
Valsartan (API)	1000	1000	1000	1000	1000	1000	1000	1000
PEG 600	25	75	25	75	25	75	25	75
PG	25	25	75	75	25	25	75	75
PEG 400	20	20	20	20	60	60	60	60
Tween 20	25	25	25	25	25	25	25	25
Lactose	850	850	850	850	850	850	850	850
PVP	85	85	85	85	85	85	85	85
MCC	250	250	250	250	250	250	250	250
Na Lauyral Sulfate	25	25	25	25	25	25	25	25
Talc	25	25	25	25	25	25	25	25
Magnesium Stearate	25	25	25	25	25	25	25	25
Total Weight	2355	2405	2405	2455	2395	2445	2445	2495

* Ingredients are calculated for the preparation of 12 capsules per formulation (or their multiples).

Table 3-1b: Designed Formulation (F9-F14) using central composite design, respective constituents and quantity

Ingredients* (mg)	F9	F10	F11	F12	F13	F14
Valsartan (API)	1000	1000	1000	1000	1000	1000
PEG 600	7.96	92.04	50	50	50	50
PG	50	50	7.96	92.04	50	50
PEG 400	40	40	40	40	6.36	73.64
Tween 20	25	25	25	25	25	25
Lactose	850	850	850	850	850	850
PVP	85	85	85	85	85	85
MCC	250	250	250	250	250	250
Na Lauyral Sulfate	25	25	25	25	25	25
Talc	25	25	25	25	25	25
Magnesium Stearate	25	25	25	25	25	25
Total Weight	2382.96	2467.04	2382.96	2467.04	2391.36	2458.64

* Ingredients are calculated for the preparation of 12 capsules per formulation (or their multiples).

Table 3-1c: Designed Formulation (F15-F20) using central composite design, respective constituents and quantity

Ingredients* (mg)	F15	F16	F17	F18	F19	F20
Valsartan (API)	1000	1000	1000	1000	1000	1000
PEG 600	50	50	50	50	50	50
PG	50	50	50	50	50	50
PEG 400	40	40	40	40	40	40
Tween 20	25	25	25	25	25	25
Lactose	850	850	850	850	850	850
PVP	85	85	85	85	85	85
MCC	250	250	250	250	250	250
Na Lauyryl Sulfate	25	25	25	25	25	25
Talc	25	25	25	25	25	25
Magnesium Stearate	25	25	25	25	25	25
Total Weight	**2425**	**2425**	**2425**	**2425**	**2425**	**2425**

* Ingredients are calculated for the preparation of 12 capsules per formulation (or their multiples).

Results and Discussion

3. Pre-formulation studies (Identification of Valsartan)

3.1.1 Melting point determination

In the present study the melting point of valsartan were determined and found to be 115 °C. The melting point of drug was in accordance with the pharmacopoeial value.

3.1.2 Water Content (Karl Fischer Method)

The percentage of water content was determined using the Karl Fischer apparatus. Valsartan contains 0.2% of water (which is within the USP specifications mentioned in the pharmacopeia i.e. not more than 2.0 %, w/w).

3.1.3 Specific Rotation

The specific rotation of valsartan (as of anhydrous substance in methanol) was found -67.0° (-68.0°, Saydam and Takka, 2007), which ascertain the purity of the valsartan used.

3.1.4 Ultra violet (UV) spectroscopy

The scanning of valsartan in methanol and buffer 6.8 using the UV spectrometer was within a wave length range of 200 - 350 nm where peaks were detected as shown in Figure 1-2 (Appendix). The maximum absorbance of valsartan (λ_{max}) was observed at 250 nm,which is identical to the certificate of analyses provided by the manufacturer and are in accordance with the pharmacopoeial data. The above results confirmed that the sample was pure as sharp and satisfactory peaks were observed.

The scanned spectra of the drug and other excipients indicate that there was no interference from the excipients in the analysis of the drug, since these are having different λ_{max} values.

3.1.5 IR Infrared spectroscopy

The valsartan was identified using infra red spectroscopy, see Figure 3 (Appendix), and the IR spectroscopy data revealed that they were in accordance to those recorded in the pharmacopeia. The IR spectroscopy data ascertain the identity and purity of valsartan. The following peaks were observed in both spectrum of Valsartan; 3059 cm^{-1} (N – H stretching), 2961.13 cm^{-1} (C – H stretching), 1732 cm^{-1} due to C = O stretching (COOH), 1605 (C=C); 1473, 1411 1273, 759 cm^{-1}. FTIR spectrum showed that the characteristics bands of sample of Valsartan were similar to that of reference spectrum of Valsartan found in European Pharmacopoeia.

3.1.6 Drug content evaluation by High Performance Liquid Chromatograph (HPLC)

The percent purity of raw material and drug content of the prepared formula was carried out by HPLC (Shakya, AK, 2016). The calibration standard of valsartan (1.25-64.0 µg/ml) were prepared in mobile phase using stock solution of valsartan, calibration curves using HPLC were constructed and are presented in the Appendix (Figures 4). The regression equation and the regression coefficient are mentioned in the Table 4.1. The chromatogram of pure valsartan and valsartan sample from formulation is given in appendix (Figure 5a –b).

3.1.7 Drug-excipients interaction

3.1.7.1 IR (Infrared) spectroscopy:

The interaction of drug with different excipients was checked using FT-IR spectroscopy (Appendex, Figure 6-9). careful examination of FT-IR spectra indicate that there were no chemical interaction between the valsartan and the excipients like SLS, MCC, PVP and lactose. The suppression of signal was observed which might be due to the presence of moisture in the excipients and the recording condition (Attenuated total reflectance mode).

The drug content was evaluated by the HPLC method, which also indicates that there were no interaction (no adduct formation or secondary signals) between the excipients and drug. Hence it can be concluded that the excipients were compatible with drug. The IR spectra of optimized formulation also suggest that there were no chemical interaction between the components. No degraded products or adducts were detected in the HPLC-PDA analysis (200-350nm). Valsartan and other excipients were also compatible, so these excipients can be used for the formulation. The IR spectra of valsartan and optimized formulation is given in Appendix (Figures 10) indicating no chemical interaction with the excipients.

3.1.7.2 HPLC (High Performance Liquid Chromatography)

Valsartan was analyzed alone and in formulation using in-house developed method. No drug-excipients interaction was observed as the retention times for valsartan was consistent and no new product / degraded products or adducts were observed during analysis using HPLC-PDA (photo diode array) (Shakya, AK, 2016).

Table 4.1: Calibration curve for valsartan

Concentration (µg/ml)	Mean peak Area
1.25	**10876**
2.5	**21374**
5	**42510**
10	**83782**
15	**126676**
25	**213958**
40	**344971**
50	**424866**
64	**547795**
y=8559.82(±66.8)x - 476.95(±496.0) (r=0.9999)	

* Ingredients are calculated for the preparation of 12 capsules per formulation (or their multiples).

Table 4.3: Dissolution rate of valsartan from prepared formulation (F1-F15), marketed formulation and from API

Time	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15	Modified F5	Dio van	Val (API)
0.5	30.6	27.9	32.2	31	39	31.1	15.4	16	26.4	23.6	29.8	18.1	24.1	20.8	14.7	45.0	92.0	0.5
1.0	40.8	35.4	44.2	42.6	52.4	42.5	23	23.5	36.1	29.5	38.3	24.2	31.6	29.6	22.6	74.2	93.0	5.2
1.5	52.2	45.2	55.6	53.2	62.6	51.4	29.5	31.5	44.3	37.6	48.7	32.2	41.5	41.6	31.1	80.2	95.0	10.7

2.0	61.7	55.3	67.9	64	72.8	59.6	35	39.9	53.4	45.6	56.8	41	54.2	53.4	37.8	86.2	96.0	14.2
2.5	70.1	62.8	75	72	78.5	66.7	40.2	45.5	58.6	51.5	62.3	46.3	59.2	61.3	41.5	86.5	99.9	18.3
3.0	78.4	70.4	82.1	79.9	84.2	73.9	44.3	51.1	63.2	55.9	67.3	52.1	64.8	68.5	45.2	86.9	99.9	19.1
3.5	86	81.4	89.9	88.7	90	81.3	48.5	53.2	68	59.5	72.2	57.7	69.8	74.0	50.0	86.8	99.9	19.9
4.0	92.1	88.1	97.4	96.9	94.6	88.7	52.8	54.1	72.8	63.3	77.0	63	75.6	78.8	55.6	86.8	-	23
4.5	96	92	99	99	98	92	56.6	54.6	77.2	67.7	81.4	67.9	79	83	59.1	90.1	-	27.1
5.0	99	96	99.5	99.5	99	94	59.6	57.7	81.1	71.8	85.1	72.4	83	85.8	63.0	92.0	-	29.7
5.5	99.9	99.5	99.5	99.5	99.5	99	63	60.3	84.9	75.5	88.8	76.6	86.6	88.4	65.9	95.0	-	32.8
6.0	99.9	99.8	99.5	99.5	99.5	99.5	66	62.7	88.9	79	91.8	80.3	89.4	89.4	68.4	98.0	-	35.2

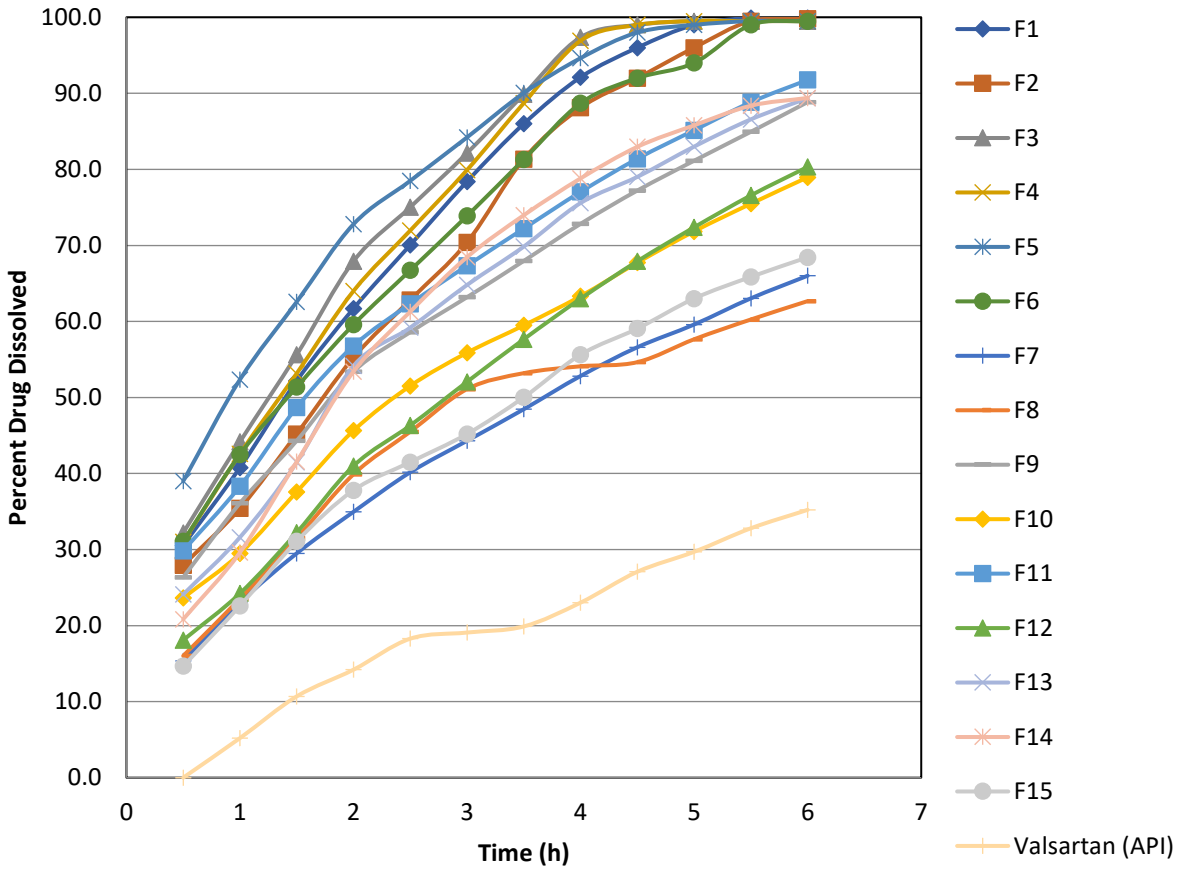

Fig. 4.1. Percent drug dissolved versus time (h) profile of the different formulations of Valsartan and API.

Table 4.4. Factor level and observed responses (Percent drug released at time T_{60}, T_{90}, T_{120} and T_{180}) in Central Composite design for 20 experimental trial

					% Valsartan dissolved at time (min.)			
Std	**Type**	**A: PEG600**	**B: PG**	**C: PEG400**	**T_{60}**	**T_{90}**	**T_{120}**	**T_{180}**
1	Factorial	25	25	20	40.8	52.2	61.7	78.4
2	Factorial	75	25	20	35.4	45.2	55.3	70.4
3	Factorial	25	75	20	44.2	55.6	69.7	82.1
4	Factorial	75	75	20	42.6	53.2	64.2	79.9
5	Factorial	25	25	60	52.4	62.6	72.8	84.2
6	Factorial	75	25	60	42.5	51.4	59.6	73.9
7	Factorial	25	75	60	23.1	29.5	35.5	44.3
8	Factorial	75	75	60	23.5	31.5	39.9	51.1
9	Axial	7.955	50	40	36.1	44.3	53.4	55.2
10	Axial	92.045	50	40	29.5	37.6	45.6	55.9
11	Axial	50	7.955	40	38.3	48.7	56.8	67.3
12	Axial	50	92.045	40	24.2	32.2	41.1	52.1
13	Axial	50	50	6.364	31.6	41.5	64.2	64.8
14	Axial	50	50	73.636	29.6	41.6	53.4	68.5
15	Center	50	50	40	22.6	31.1	37.8	45.2
16	Center	50	50	40	22.8	31.9	38.2	53.2
17	Center	50	50	40	23.4	32.5	36.7	47.1
18	Center	50	50	40	24.1	31.1	36.1	50.1
19	Center	50	50	40	32.1	35.2	40.1	55.7
20	Center	50	50	40	36.2	32.9	42.3	60.5

A, B, C – quantity of excipients for the preparation of 12 capsules

Table 4.5 : ANOVA for response surface reduced Quadratic Model for percent drug dissolved at time 120min.

(Analysis of variance table partial sum of squares - Type III]

Source	**Sum of Squares**	**df**	**Mean Square**	**F Value**	**p-value Prob > F**	
Model	2688.17	7.00	384.02	26.35	**< 0.0001**	**Significant**
A-PEG600	83.74	1.00	83.74	5.75	0.0337	
B-PG	323.85	1.00	323.85	22.22	0.0005	
C-PEG400	274.82	1.00	274.82	18.86	0.0010	
BC	682.65	1.00	682.65	46.84	< 0.0001	
A^2	323.51	1.00	323.51	22.20	0.0005	
B^2	297.50	1.00	297.50	20.41	0.0007	
C^2	928.34	1.00	928.34	63.70	< 0.0001	
Residual	174.88	12.00	14.57			

Lack of Fit	148.31	7.00	21.19	3.99	**0.0736**	**Not significant**
Pure Error	26.57	5.00	5.31			
Cor Total	2863.05	19.00				

3.4 Conclusion :

The poorly soluble drug valsartan can be released effectively from the simple developed capsule formulation by utilizing the co-solvent system (PEG600/PG/PEG400) containing a $KHCO_3$ (2.1 % w/w) and other excipients in formulations.The dissolution rate profile of the formulation was improved when compared to the valsartan alone.The rate of release valsartan from formulation F-5 was more than 72% after 2 hours, while the formulation F-7 showed only 35% of drug release. Formulation F-5 was further improved by the addition of $KHCO_3$ (2.1 w/w %), which releases 86% valsartan in-comparison to marketed formulation Diovan (96%). Fourier transforms infrared spectroscopy (FT-IR) and HPLC indicate that there were no interaction between the valsartan and the excipients used. No adduct formation or degraded products were observed using HPLC. The stability studies were carried out as per the ICH guidelines. The formulations were stable during the study period.All formulations showed appreciable stability up to 6 months (at room temperature) without undergoing any degradation. However, in formulation number F7, F8, and F9. Showed some discoloration after a period of 3 months. The formulation was effectively optimised using the central composite design which is very commonly used for formulation development.Finally it can be concluded that developed formulation of valsartan is stable and can be further improved for routine purpose on the basis of current data.More studies like in-vivo could help in the development of the formulations.

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