FORMULATION AND EVALUATION OF FAST DISSOLVING TABLET OF VALSARTAN BY USING MIXED HYDROTROPY TECHNIQUE

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ABSTRACT
The purpose of this labor is to create and assess quick-dissolving pills of Valsartan utilizing the mixed hydrotropy concept to enhance its solubility and dissolution rate. Valsartan, an antihypertensive agent, exhibits poor aqueous solubility, posing challenges in achieving prompt therapeutic action. The mixed hydrotropy approach leverages a combination of hydrotropic agents to improve solubility and bioavailability. In this study, Nicotinamide, Sodium benzoate, Ammonium acetate, Sodium acetate and Lactose were selected as hydrotropic agents and incorporated into the tablet's makeup. After the tablets were prepared using the simple compression method, we evaluated the formulations based on pre-compression properties like bulk density, tapped density, and compressibility index. Evaluations were conducted on post-compression parameters, including hardness, friability, weight variation, wetting time, water absorption ratio, in vitro dispersion time, and drug concentration, to ensure tablet quality and uniformity. The efficacy of the mixed hydrotropy strategy has been demonstrated by in vitro dissolving studies, which demonstrated a significant increase in the rate of valsartan dissolve from the FDTs in comparison to pure medicine and conventional tablets. Differential

Scanning Calorimetry (DSC) analyses indicated no significant drug-excipient interactions, ensuring the stability of the formulation. In conclusion, the mixed hydrotropy approach proved to be a viable and efficient method to increase the rate of solubility and dissolved Valsartan, leading to successful development of fast dissolving tablets that could potentially improve patient compliance and therapeutic efficacy in hypertension management.

INTRODUCTION

Oral ingestion is the greatest practical and widely used form of medication delivery because of its low cost, variable dosage type, high patient compliance, convenience of administration, and lack of sterility limitations. Consequently, there is an increased likelihood of many generic medication manufacturers producing oral drug products that are bioequivalent. But the primary issue with oral dosage form design is that these forms have low bioavailability. Several factors, such as the permeability of drugs, water-soluble, first-pass metabolic processes, dissolving rate, pre-system metabolism, and mechanism of sensitivity to efflux, affect oral bioavailability. The most typical factors of limited oral bioavailability are inadequate permeability and poor solubility[1]. Solubility is also crucial for parenteral formulations and other dosage forms[2]. Solubility is one important component in defining the optimal drug concentration in systemic circulation and the pharmacological response that follows[3]. Poorly water-soluble drugs also needed high dosages after oral administration to achieve therapeutic plasma concentrations. A common issue in the development of novel chemical entities and generics is their low solubility in water. At the absorption site, every drug that must be absorbed needs to be there as an aqueous[4]. The best solvent for medicinal formulations that are liquid is water. Most medications have little solubility in water and are either mildly basic or weakly acidic[4-5]. The pharmaceutical industry produces roughly 40% of its NCEs (new chemical entities) that are water insoluble. There is gastrointestinal mucosal toxicity and sufficient and variable bioavailability because of these weakly water-soluble, slowly absorbed medicines. Above all, for oral medications, solubility is a fundamental single-rate limiting factor because it makes it easier to obtain the amount that the body needs to absorb to produce a pharmacological reaction. Solubility is a big problem for formulation scientists[6-8]. A homogeneous solvent solution can be produced by dissolving a component known as a solvent in another substance, which can be solid, liquid, or gaseous. This quality is known as solubility. In general, temperature, pressure, and the type of solvent employed all affect how soluble the medication is. Saturation concentration is a measure of a product's solubility in a solvent when more solvent is added without raising the concentration of the mixture[9].As stated by IUPAC, solubility refers to the amount of a given solute in each solvent or the saturation point at which a solution is analytically composed. Concentration, mole, ratio of moles, mole fraction, and additional quantities are among the solubility measuring units[10]. Typically, Solubility constants are defined by using saturated solutions of ionic substances that are poorly soluble. This has to do with an equilibrium mechanism. The ratio of the dissolved salt to the dissolved salt ions was given. To predict intestinal medicine absorption, the food and medicine administration of the United States developed the Biopharmaceutical Classification System (BCS). This method limits prediction by utilizing the intestinal permeability and solubility parameters[10-12].

With low aqueous solubility, most medication compounds are lipophilic[9-11]. Scientist Carl A. Neuberg first described anionic organic salts as "hydrotropy" in 1916. He said that materials that could make something "water-soluble" would be referred to as "hydrotropic

materials." Improving the water solubility of inert compounds is a method for co-solving pharmaceuticals that are poorly soluble in water with other highly soluble compounds.
Hydrotropes, such as urea, sodium citrate, sodium acetate, sodium benzoate, and nicotinamide, are substances used to enhance drug solubility in weakly soluble aqueous media. Hydrotropic combinations may be applied to increase the soluble of substances those are not very water-soluble since coupled hydrotropic solubilizers have a synergistic or cumulative impact. Hydrotropes can assist a sparsely soluble organic molecule become more soluble in water. It is a technique that helps make solutes that are poorly soluble in water more soluble by adding a second solution (hydrotrope). A hydrotropic molecule can attach itself to a less water-soluble substance by attractive interactions between dipoles. When there is a significant amount of another solvent present, one solvent becomes more soluble[11-12].
Fast dissolving drug delivery system is becoming more and more popular as innovative medication administration methods since they are simple to use and increase patient motion sickness, unexpected episodes of coughing or allergic reactions, and a lack of water[12]. Given that this problem affects both young and elderly patients. Therefore, as an alternative dose form, fast-dissolving orally-disintegrating tablets have arisen to address these issues. To increase patient compliance, recent developments in innovative drug delivery systems (NDDS) seek to enhance a medicine's safety while preserving its therapeutic value. Efforts have been undertaken by pharmaceutical technologists to create a drug delivery system that dissolves or disintegrates quickly (FDDT)[11-13].

MATERIAL AND METHODS

Mylan Laboratories, Sinnar, Nashik, has provided a complimentary sample of valsartan. We purchased nicotinamide, lactose, sodium benzoate, and sodium acetate from Modern Industries in Nashik. The remaining reagents were all analytical grade and were acquired from Thermo Fisher Scientific India Pvt. Ltd.

Valsartan hydrotropic solid dispersion

To make the dispersion of hydrotropic solids, precisely weighed amounts of each ingredient were added to 100 milliliters of beaker together with 1.5 grams of nicotinamide, 0.5 grams of sodium acetate, and 0.5 grams of ammonium acetate[15-16]. Also included was the bare minimum of distilled water that is warm required to make the hydrotropic mixture. Drug's chemical stability won't be harmed throughout the water removal process if the minimal amount of water roughly 5 milliliters is utilized. It will also take less time to evaporate. Using two magnetic rice beads coated in Teflon and a high-speed magnetic stirrer, the hydrotropic mixture was made to dissolve more easily[17]. One gram of valsartan (drug to carrier ratio: 1:4) was dissolved in the solution after the hydrotropic combination above had fully dissolved[18-20]. The temperature was maintained between 55 and 60°C to help with water evaporation. Rice has a higher viscosity than water, thus when the water evaporates, the rice magnetic bead naturally slows down and stops swirling, signaling the formation of a wet hydrotropic solid dispersion[20-22]. Several watch glasses were coated with the resultant moist solid dispersion and put within a dry heat-air oven that was kept fifty degrees Celsius[25]. This allowed for easy evaporation of any residual moisture and the maintenance of a constant weight without any additional weight loss from evaporation[26]. The Dispersions of hydrotropic solids were pounded in a pestle made of glass and mortar, filtered via sieve number sixty, and sealed within a glass bottle after being allowed to dry fully[27].

Table 1: Formulation batches of valsartan

Components	F_1	F_2	F_3	F_4	F_5	F_6	F_7
Valsartan solid dispersion	1:4	1:1	1:4	1:4	1:1	1:1	1:4
Crosspovidone: SSG	1:4	1:1	1:1	1:1	1:4	1:4	1:4
MCC	106	50	50	106	106	50	50
Magnesium Stearate	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2

RESULT AND DISCUSSION

Saturated valsartan solubility in purified water:

Valsartan's saturated solubility in distilled water was determined to be 0.02937 ug/ml.

Equilibrium solubility studies in different hydrotropic agents: Table 2 displays the evaluation of Valsartan's equilibrium solubility in several hydrotropic solutions. Valsartan's solubility can be improved by all hydrotropes. 40% of the nicotinamide solution was found to have the highest valsartan solubility.

Table 2: Studies of equilibrium solubility in various hydrotropic compounds

No.	Hydrotropic solution	Valsartan solubility (mg/ml)				
		5%	10%	20%	30%	40%
1	Sodium Acetate	1.46	1.28	2.76	2.18	0.003
2	Nicotinamide	105.9	525.0	364.7	513.8	2164.1
3	Lactose	0.103	0.011	0.001	0.061	0.117
4	Sodium benzoate	14.00	3.084	5.244	7.591	29.32
5	Ammonium Acetate	1.68	3.425	1.951	1.041	0.120

Among the different hydrotrope used, solubility of Valsartan was found to be higher in Nicotinamide (40%) > Sodium benzoate (40%) > Ammonium acetate (10%) > Sodium acetate (20%) > Lactose (40%).

Solubility enhancement ratio determination:

Valsartan's solubility enhancement ratio in a range of hydrotropic solutions was calculated; the findings are shown in Table 3.

Table 3: Solubility enhancement ratio determination

No.	Hydrotropic solution	Solubility enhancement ratio of valsartan				
		5 %	10 %	20 %	30 %	40 %
1	Sodium Acetate	49.85	9.862	94.26	74.44	0.111
2	Nicotinamide	3948.3	17515.6	12320.4	1807.51	70276.6
3	Lactose	3.511	0.394	0.059	2.087	3.9724
4	Sodium Benzoate	511.0	105.0	178.5	258.4	938.59
5	Ammonium acetate	57.318	106.64	66.45	35.43	4.108

Among the different hydrotrope used, solubility of Valsartan was found to be higher in Nicotinamide(40%w/v)>Sodiumbenzoate(40%w/v)>Ammoniumacetate(10%w/v)>Sodium acetate(20%w/v)>Lactose (40%w/v).

Valsartan was therefore shown to be most soluble in 40% w/v nicotinamide solution, with a solubility enhancement ratio of 70,286 as compared to water.

Equilibrium solubility of Valsartan in mixed hydrotropic blends:

The hydrotropic combinations were used to create mixed hydrotropy blends of hydrotropic agents. The findings of determining Valsartan's solubility in mixed hydrotropic blends are presented in Table 4.

Table 4: Equilibrium solubility of Valsartan in mixed hydrotropic blends

No.	Hydrotropic combination	Total concentration (%w/v)	Ratio	Solubility (mg/ml)	SER
1	N+SB+AA+SA	40	10: 10: 10: 10	33.92	1155.2
2	N+SB+AA+SA	40	5: 5: 15: 15	230.8	7859.8
3	N+SB+AA+SA	40	15: 5: 5: 15	26.65	907.4
4	SB+AA+SA	40	15: 15: 5: 5	272.1	9163.2
5	N+SB+AA+SA	40	5: 15: 15: 5	29.90	1018.2

Nicotinamide (N), Sodium benzoate (SB), Ammonium acetate (AA), and Sodium acetate (SA).

Differential scanning calorimetry

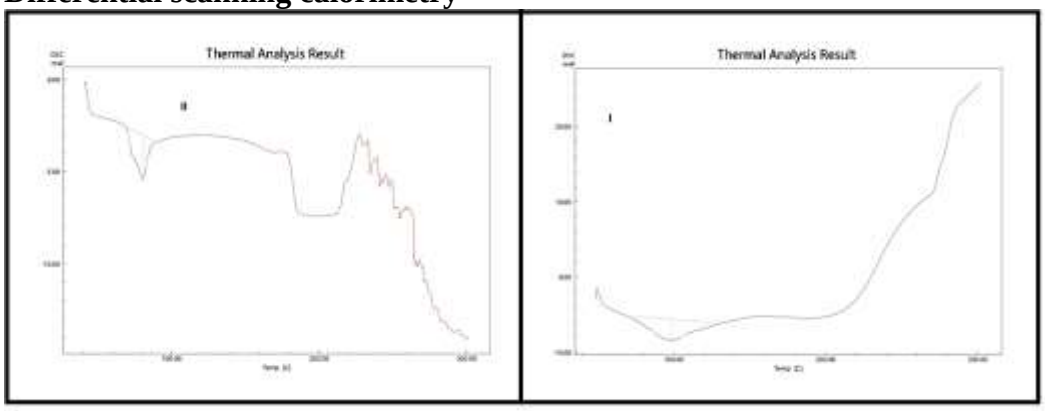

Figure 1: DSC of Valsartan and Physical Combination

The figure I displays DSC thermogram for Valsartan were revealed a strong endothermic peak at 98.29 C, this is the same as the drug's melting point and verifies its purity. After it melted, the medication did not break down. The figure II displays DSC thermogram for physical mixture were revealed at 80.89º C, a strong melting endotherm was observed. Drug melting peak at 80.89º C and broad endothermic peak at sharp melting endotherm were found.

Pre-Compression Characteristics

Table 5: Pre-compression characteristics of powder mixture

Formulation code	Bulk density (g/cm3)	Tapped density (g/cm3)	Angle of repose (Ɵ)	Hausner's ratio	Carr's index (%)
F_1	0.47	0.55	28.14	1.14	14.54
F_2	0.44	0.49	22.05	1.09	1.09
F_3	0.49	0.70	24.12	1.13	21.42
F_4	0.55	0.62	26.92	1.13	12.90
F_5	0.53	0.71	23.04	1.13	23.72
F_6	0.55	0.72	27.77	1.13	17.24
F_7	0.51	0.58	27.85	1.13	21.76

Post-Compression Characteristics

Thickness: The breadth of the formulations was evaluated using "Vernier caliper". Every tablet was put between two anvils to determine its thickness. The sliding knob was then adjusted until the tablet fit snugly, and the measurement was then recorded. Ten tablets were chosen at random.

Hardness: The "Monsanto hardness tester" conducted the test. The typical hardness for a formulation ranges from 2.0 to 3.5 kg/cm2. This guarantees that every formulation batch has good handling qualities.

Friability: The tablets' friability is determined to evaluate how resistant they are to abrasion during handling, packaging, and transportation. To assess the malleability of the produced tablet, the "Roche friabilator" used. Using a Roche Friabilator, the friability of ten tablet samples was evaluated. For four minutes, ten pre-weighed tablets were spun at 25 rpm. The pills were weighed again using a 60-mesh filter after the particles were removed, and the weight reduction percentage was computed. (Weight loss / starting weight) x 100 = % Friability. A % friability analysis was conducted on all fast-dissolving tablet formulations. The pharmacopoeial limit is found to be within the range of 0.6134% which is the average percentage friability for formulations.

Weight variation: An electronic balance is accustomed to determine the mean weight of twenty pills. Every tablet weight is determined individually and contrasted with the average weight. If there are no more than two tablets that deviate from the % restriction and if there are No tablets that deviate from the prescribed proportion by more than twice, the tablets meet USP requirements.

Disintegration Time: A tablet disintegrating into tiny bits is referred to as disintegration. To determine time of in vitro disintegration, disintegration test equipment was used in compliance with I.P. norms. Fill the six tubes in the basket with one tablet each. Insert a disc into each tube and operate the device with an immersion liquid (immersion simulated saliva fluid) maintained at 37°C and pH of 5.8. Thirty times a minute at 37± 2°C and a pH of 5.8, the assembly must be lifted and lowered. The number of seconds needed for the pill to entirely dissolve and leave no observable mass inside the apparatus was computed and recorded.

Table 6: Post-compression characteristics

Formulation Code	Hardness (kg/cm^2)	Friability (%)	Thickness (mm)	Weight variation (mg)	Disintegration time (Sec.)
F_1	2.9	0.45	2.14	159.63	29.16
F_2	2.8	0.81	2.05	158.18	24.16
F_3	2.9	0.70	2.12	158.33	16.16
F_4	2.8	0.61	2.92	160.1	20.54
F_5	3.1	0.71	2.04	159.02	35.44
F_6	3.0	0.72	3.77	162.02	46.61
F_7	3.2	0.58	2.85	158.02	55.12

In vitro dissolution study: A USP Type-II equipment was utilized to evaluate the dissolving rate at 50 rpm when 900 ml of buffer pH (5.8) (simulated saliva fluid) was used as the dissolve medium. The dissolving media was maintained at 37 ± 2°C, and an aliquot was taken and filtered out every ten minutes. The concentration of the medication was

ascertained by measuring the absorbance of the filtered solution at 250 nm using a UV spectrophotometric method using a standard calibration curve.

Table 7: % Drug release of F1-F7

Time	F_1	F_2	F_3	F4	F_5	F_6	F_7
0	0	0	0	0	0	0	0
10	12.89	13.01	14.02	15.68	16.18	17.19	18.19
20	30.85	31.87	32.89	33.93	34.95	35.93	36.94
30	49.00	49.04	50.01	51.14	52.15	53.10	54.50
40	61.40	61.40	62.41	63.42	64.45	65.49	66.48
50	70.35	71.38	72.39	73.41	74.42	75.82	76.85
60	80.44	81.44	82.45	83.47	84.49	85.59	87.59
70	84.31	85.38	86.39	87.41	88.42	89.43	90.49
80	87.17	88.18	89.19	90.18	91.19	90.10	91.10
90	91.35	91.35	92.36	93.37	93.82	94.88	95.88

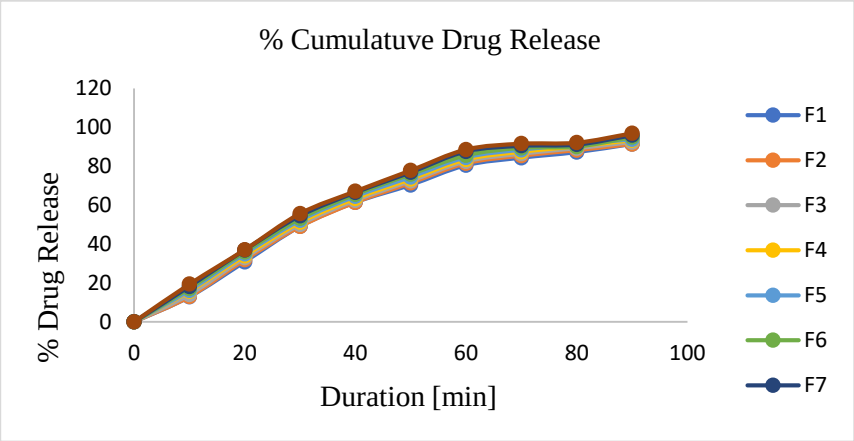

Figure 2: Dissolution Profile F1-F7

CONCLUSION

The goal of the current study was to boost Valsartan's solubility by applying the mixed hydrotropy approach. The oral hypertension medication valsartan has a limited bioavailability and a poor solubility in water. A safe, environmentally friendly, cutting-edge, and affordable method to improve the bioavailability of medications that aren't very soluble in water is the mixed hydrotropy concept. After being received as a gift sample, valsartan was examined using FTIR, UV spectroscopy, solubility, melting point, and organoleptic qualities to ensure that it met all requirements. The 40% nicotinamide solution showed the maximum valsartan solubility in terms of equilibrium solubility in individual hydrotrope solutions. The solubility of valsartan was shown to be enhanced around 960 times with a blend of hydrotropic compounds that are combined with a 15+15+5+5 the nicotinamide ratio, ammonium acetate, sodium acetate, and sodium benzoate.

In DSC studies of drug valsartan and its physical combination, there were no interactions between drug and its excipients. Low aqueous solubility was the limitation for formulation of valsartan, mixed hydrotropy approach resulted in enhancement of aqueous solubility, and this may further enhance dissolution rate and bioavailability of valsartan on oral administration. The enhanced solubility may further reduce dose or frequency of administration of valsartan.

CONFLICT OF INTEREST: The authors have no conflicts of interest regarding this investigation**.**

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