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A REVIEW ON COMPARISON OF DIFFERENT TECHNIQUES USED TO ENHANCE DISSOLUTION OF VALSARTAN AND TELMISARTAN ORAL SOLID DOSAGE FORM

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ABSTRACT

Telmisartan and Valsartan are strong angiotensin-II type 1 receptor inhibitor, applied in the care of elevated blood pressure. Telmisartan and also Valsartan comes under Class II category of BCS classification. Valsartan and Telmisartan both are highly pH dependent and poor soluble drug which result in improper absorption and low bioavailability (43% and 23% respectively). In order to control the poor solubility as well as bioavailability of both Telmisartan and Valsartan, different formulation techniques are compared on the basis of dissolution. In this review article, solid dispersion by kneading method, pelletization by pan coating, modified microcrystalline cellulose (MCC) pellets and solid self-micro-emulsifying drug delivery system (SMEDDS) formulation techniques are discussed for Telmisartan. Whereas, in case of Valsartan, liquisolid compact technique, fast disintegrating tablets (FDT), and formulation optimized by 23 factorial designs are evaluated. To sum up, the analogy of Telmisartan formulations demonstrates that solid dispersion (TS5) and fast dissolving pellet formulation (TP3), both the techniques showed better drug release profile than MCC pellet and SMEDDS techniques. However, when it comes to dissolution rate, fast dissolving pellet formulation reflects notably best results among all. Furthermore, Valsartan formulation techniques evaluation leads us to conclude that liquisolid method showed good release profile as compare to conventional products but the method incorporates some complex requirements of load factor calculation and saturation solubility studies. In addition to that, Valsartan formulation optimized by factorial design as well as fast dissolving tablet (FDT) formulation signifies more conventional approach as well as good drug release profile.

Keywords: Telmisartan, Valsartan, pelletization, modified microcrystalline cellulose (MCC), self-micro-emulsifying drug delivery system (SMEDDS), Fast Disintegrating Tablets (FDT).

INTRODUCTION

High blood pressure is regarded as a global health issue. It is a condition with surge in blood pressure. Moreover 25% of adults are affected by hypertension **[1]**. According to recent guidelines of Hypertension, angiotensin-converting enzyme (ACE) inhibitors, diuretics, calcium channel antagonist (CCBs)and angiotensin receptor blockers (ARBs) are considered as primary antihypertensive treatment for many patients.[2] Due to factual based findings of clinical efficacy, individual with either stage(I-II) hypertension and also with either types (1 or 2) of diabetes, ACE inhibitors or ARBs are suggested **[2]**.

Generally, Valsartan and Telmisartan (TEL) are potent, long-lasting inhibitors of angiotensin-II receptor type 1 (AT1). Research shows that in evaluation with other angiotensin-II receptor type1 blockers, TEL appeared to have foremost binding affinity towards type 1 receptor; whereas, Valsartan tends to display 20,000 times greater affinity towards type 1 receptor than type 2 **[3, 4]**. TEL is basically useful in the management of high blood pressure and averts renal insufficiency produce by diabetes and congestive heart failure **[5, 6]**. Besides this, clinical grounds display affectivity of TEL in reducing atrial fibrillation (A-fib) recurrence, arterial stiffness and left ventricular hypertrophy (LVH) **[7]**. FDA has approved Valsartan for the therapy of increased blood pressure in children more than six years old **[8]**. Additionally, Valsartan aids in maintaining renal function, so it can be prescribed for those hypertensive patients who are suffering with renal insufficiency **[9]**. Along with the antihypertensive outcome of Valsartan therapy, its cardio protective effects exhibit beneficial outcomes in terms of heart failure (HF) and myocardial infarction (MI) related co-morbidities **[10]**. Both are used as monotherapy for blood pressure management and also in conjunction with other antihypertensives as both exhibit high tolerability profile **[11-14]**. Moreover, because of once daily dosing regimen of TEL and Valsartan, good patient compliance is achieved **[15, 16]**.

Valsartan and TEL are classified to BCS Class II entities. They possess less water solubility <0.001g/ml and 0.09 g/mL respectively, and dissolution rate-restricted absorption. Both are also greatly ionizable and has pH-dependent solubility **[17, 18]**. TEL is only moderately soluble in fully acidic media but not so much in strong alkaline media. Whereas, Valsartan is slightly acidic, hence it is imperfectly solubilized in the low pH where it is need to be absorbed **[19-21]**. So, the concern about Valsartan and TEL that both are highly pH dependent and poor soluble drug, resulting in improper absorption and low bioavailability (43% and 23% respectively) **[22, 23]**.

Several techniques regarding formulation have recently been devised to direct the challenges of less water solubility and poor availability of drugs to the accessing site of drug correlated to BCS Class II entities like;

prodrug preparations, self-emulsifying approach, salt preparations, milling method (micro/nano-scale composition), oral oil-based preparations, cyclodextrin composites, solid dispersion (SD) and liquisolid (LS) compaction technique **[24-27]**.

In this review article we compare the different formulations techniques has been utilized to control the low solubility issue linked with Valsartan and TEL. Moreover, the review gives a healthier knowledge of the above-mentioned technologies in developing oral solid dosage forms associated with inadequately water-soluble and ionized drugs. This article will deliver considerable insight into the direction of these techniques on the solubility and rate of dissolution of Valsartan and TEL oral solid dosage forms.

METHOD

In order to review different approaches for increasing the solubility and dissolution characteristics of Valsartan and Telmisartan oral solid dosage form, essentially, the data was gathered from literature published within the last twenty years (2000 to 2020). The databases used to collect the published literature relating to diverse approaches used to enhance dissolution of Valsartan and Telmisartan were Google scholar, ScienceDirect, Scopus PubMed, ResearchGate, MDPI pharmaceutics, NIH, JGTPS. From these databases almost 20 articles were computed. Abstracts were reviewed of downloaded articles; 7 articles were rejected after careful review of Abstract. After this screening, detailed review was done for remaining articles. Results were evaluated and tabulated, compared with publications of different authors and conclusions were made. Articles were also evaluated for their quality in terms of type of journal, where it has been published, data collection methods, statistical tests, significance values and interpretations made.

Inclusion Criteria

Articles related to Valsartan and Telmisartan intrinsic solubility, physicochemical evaluation, bioavailability, oral solid dosage forms, dissolution enhancement techniques.

Exclusion Criteria

Articles related to Valsartan and Telmisartan's synthesis, clinical efficacy, adjuvant therapies, salt preparation, modified/sustained release formulations, liquid dosage forms.

RESULTS AND DISCUSSION

Telmisartan

Telmisartan's solid dispersion and fast dissolving pellet formulations techniques show higher drug release of formulation TS5 and TP3 **[28]** Also, these formulations were found stable during stability conditions. However, it was noticed that the dissolution rate of pellet composition (89.25–99.34%.) is greatly increased in comparison to solid dispersion technique (79.64 to 93.06%). Modified MCC Pellets of Telmisartan exhibit good release of drug but not as much as fast dissolving pellet formulation (89.25–99.34%) **[29]** The techniques of preparing liquid SMEDDS also present better release rate of drug like 100% after 120 min for

formulations SF2, SF3 and SF4, but the duration of this release is double as compare to previous techniques stability studies performed on all of the above techniques found these techniques stable. So, the fast-dissolving pellet formulation technique acquire greatest dissolution rate among all described techniques **[30]**.

Technique or method

Solid Dispersion by kneading method **[28]**

Using several concentrations of Soluplus (Co polymer) and the required amount of drug, five compositions TS1-TS5 (Table 1) have been prepared by dissolving in ethanol. It was found that the drug release of solid dispersion is increased from pure drug and marketed formulation from 45.77% -81.35% to 79.64% -93.06% respectively. The results were shown in Table 2.

Palletization by Pan Coating Method **[28]**

Five different compositions of Telmisartan pellet formulation TP1-TP5 (Table-1) have been prepared by pan coating method using crospovidone to coat sugar beads for applying medicament to beads which were further coated with HPMC. It was found that the release of drug increases to 89.25% -99.34%. The results were shown in Table- 2. So, both methods are enhancing the release of drug.

Telmisartan through modified MCC pellets **[29]**

Immediate Microcrystalline Cellulose (MCC) pellets were prepared using drug, MCC, spray dried lactose, Camphor and Croscarmellose Sodium, the results shows that the in rate of drug release increases even if the MCC used alone. So, to investigate the effect of above ingredients, factorial deign 32 (Table. 3) is used which did not affect the physical characteristics but ultimately increases the drug release. The resultant pellets were studied for shape, flow behavior, firmness, particle size examination, percent of being porous, content of drug, and ex vivo drug release after being desiccated to a sustained weight to a 50 °C. More than 80% drug release by incorporation of Croscarmellose and camphor into MCC pellets increase the drug release percentage. On the basis of above results the extrapolations derived from Design specialist. One more optimized composition (F10) was evaluated which shows the Percentage drug release of 94.25%.

Solid Self-micro emulsifying drug delivery system SMEDDS **[30]**

Thirteen doses formulated with contrasting quantities of oil, surfactant as well as co-surfactant. Using castor oil in SMEDDS is the best way to enhance the drug release and bioavailability of Telmisartan which has poor solubility. Quantity of oil and co surfactant (Propylene glycol) play significant role in enhancing the release but also over use may lead to instability of product. Optimal quantity was preferred. To increase the release rate of drug, hydrophilic surfactant (tween 20) was utilized. Each of the formulations incorporated Telmisartan in SMEDDS but to prepare solid SMEDDS (Table 4), liquid SMEDDS was mixed with MCC. The overall rate of dissolution rate

was found less because of the larger globule size but among all the formulations SF2, SF3, and SF4 displayed 100% liberation of drug as their globule size is smaller so higher will be the dissolution rates.

Valsartan dissolution enhancing techniques described above, like liquisolid compact gives increase in dissolution rate in comparison with direct compressed tablet and pure drug, but the process of liquisolid.

Valsartan

Table. 1: Solid Dispersions and Pellet Formulations Compositions of Telmisartan [28]

S. No	Ingredients (mg/10 doses)	TS_1	TS_2	TS_3	TS_4	TS_5	TP_1	TP_2	TP_3	TP_4	TP_5
1.	Telmisartan	200.0	200.0	200.0	200.0	200.0	200.0	200.0	200.0	200.0	200.0
2.	Sugar Pellets	---	---	---	---	---	2000.0	2000.0	2000.0	2000.0	2000.0
3.	Soluplus	200.0	400.0	600.0	800.0	1000.0	200.0	400.0	600.0	800.0	1000.0
4.	HPMC E5	---	---	---	---	---	50.0	50.0	50.0	50.0	50.0
5.	Crospovidone	---	---	---	---	---	50.0	50.0	50.0	50.0	50.0
6.	Ethanol	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
7.	Purified water	---	---	---	---	---	q.s	q.s	q.s	q.s	q.s

Table. 2: Telmisartan Formulations Dissolution Kinetics (In Vitro) [28]

No.	Formulations	T_{50} (min)	DE_{30} (%)	1st order		Hixon crowell	
				R^2	K_1 (min^{-1})	R^2	K_{HC} ($mg^{1/3}$)
1.	Pure drug	--	12	0.994	0.010	0.995	0.008
2.	Marketed drug	17.5	40	0.926	0.029	0.880	0.018
3.	TS_1	19	38.3	0.972	0.025	0.968	0.015
4.	TS_2	18	43.3	0.951	0.027	0.972	0.014
5.	TS_3	14	46.6	0.965	0.029	0.971	0016
6.	TS_4	9.75	55.8	0.931	0.037	0.905	0.018
7.	TS_5	9.75	60	0.940	0.043	0.903	0.021
8.	TP_1	17	43.3	0.986	0.034	0.997	0.019
9.	TP_2	9.5	53.3	0.985	0.045	0.971	0.022
10.	TP_3	9	59.1	0.958	0.076	0.989	0.032
11.	TP_4	10	56.6	0.981	0.064	0.991	0.029
12.	TP_5	10	55.8	0.991	0.055	0.976	0.026

T_{50}= Time period needed for 50% drug release; DE_{30}=Dissolution efficiency (in 30 minutes); R^2= Regression coefficient; K_1= First order rate constant; K_{HC}= Hixon crowell rate constant

Table 3: Factorial Batches Composition (F1 – F9) [29]

Batch code	Telmisartan in mg	MCC: Lactose ratio	% Camphor	%CSS	Ethanol:water ratio
F_1	20	80:20	2	4	60:40
F_2	20	80:20	2	8	60:40
F_3	20	80:20	2	12	60:40

F_4	20	80:20	6	4	60:40
F_5	20	80:20	6	8	60:40
F_6	20	80:20	6	12	60:40
F_7	20	80:20	10	4	60:40
F_8	20	80:20	10	8	60:40
F_9	20	80:20	10	12	60:40

Compact formulation is much complex, such as requirement of load factor calculation and tablet's formulation optimization by applying factorial design, results in the formulation compositions with higher drug release rate like 95.25%>85.62%>71.15% of formulations formulations Fab>F1>Fabc respectively **[31]**. Another technique discussed is fast dissolving tablet of valsartan to increase the dissolution rate of Valsartan **[32]**. Later two techniques found to be more conventional with the better outcome of optimized tablet formulation of Valsartan having conventional excipient like in FDT of Valsartan, but the dissolution rate is not described properly in FDT of Valsartan **[32]**.

Technique or method

Valsartan Liquisolid Compacts **[33]**

Propylene Glycol (PG) was used to make a variety of liquisolid compacts. The medication was first dispersed with PG before being added to the determined amounts of carrier (Avicel) and coated material (Table 5). After evaluating the graph of dissolution, it is concluded that F1-F5 formulation's tablets compressed by liquid solid compact has faster drug liberation than pure drug as well as direct compressed tablets.

Oral Tablet formulation Optimization of Valsartan by 23 factorial designs **[31]**

Using 23 factorial design Valsartan tablet formulation Table 6. was optimized to improve the dissolution of drug. Variations

were observed with different combinations binder, disintegrant and diluents. Best combination of binder, disintegrant and diluent were selected for increasing the dissolution rate. After evaluating the results, it was found that among eight, Formulation

- Fab (lactose, PVP and Primogel),
- F1 (lactose, acacia and potato starch)
- Fabc (DCP, PVP and Primogel)

Above three formulations gave higher dissolution rates 95.25%, 85.62%, 71.15% respectively.

Fast disintegrating tablet of Valsartan **[32]**

Another approach is fast disintegration tablet of Valsartan of tablets. Twelve different formulations (Table 7) were formulated using contrasting concentrations of super disintegrant e.g., Crospovidone & Sodium Starch Glycolate. Results were shown that both permit better disintegration. It was discovered that faster release of drug from FDTs can be achieved by accelerating 1% concentration to 5%, of either SSG or crospovidone.

Table 4: Composition of SMEDDS [30]

Formulations	% Oil (w/w)	% Surfactant (w/w)	% Co-surfactant (w/w)
F1	30	70	0
F2	30	60	10
F3	30	55	15
F4	40	35	25
F5	50	50	0
F6	50	25	25
F7	60	25	15
F8	60	20	20
F9	60	10	30
SMEDDS formulations transmuted to solid-SMEDDS (SF1-SF9) by utilizing adsorbent (MCC) and SMEDDS in the ratio of 1:1 w/w.			

Table 5: Valsartan liquisolid compacts Formulations [33]

Batch code	Drug concentration in PG	R	Lf	Avicel (Q= W/Lf)	Aerosil (q= Q/R)	Unit dose wt.
F1	20%	5	0.822	0.243	0.048	0.348
F2		10	0.491	0.407	0.041	0.512
F3		15	0.380	0.526	0.035	0.631
F4		20	0.325	0.615	0.030	0.719
F5		30	0.270	0.740	0.024	0.844
F6		5	0.822	0.161	0.032	0.245
F7	30%	10	0.491	0.270	0.027	0.354
F8		15	0.380	0.350	0.023	0.434
F9		20	0.325	0.409	0.020	0.492
F10		30	0.270	0.492	0.01	0.575
F11		5	0.822	0.121	0.024	0.194
F12	40%	10	0.491	0.203	0.020	0.276
F13		15	0.380	0.263	0.017	0.336
F14		20	0.325	0.308	0.015	0.381
F15		30	0.270	0.370	0.012	0.443
DCT		-	-	150	7.5	0.230

PG: Propylene glycol, DCT: Directly compressed table

Table 6: Formulations of Valsartan tablets prepared according to factorial design [23, 31]

Ingredients (mg/tab)	F1	Fa	Fb	Fab	Fc	Fac	Fbc	Fabc	F1
Valsartan	50	50	50	50	50	50	50	50	50

Acacia	5	-	5	-	5	-	5	-	5
PVP	-	5	-	5	-	5	-	5	-
Potato starch	37.5	37.5	-	-	37.5	37.5	-	-	37.5
Primo gel	-	-	12.5	12.5	-	-	12.5	12.5	-
Lactose	147.5	147.5	172.5	172.5	-	-	-	-	147.5
Di-Calcium Phosphate	-	-	-	-	147.5	147.5	172.5	172.5	-
Talc	5	5	5	5	5	5	5	5	5
Magnesium Stearate	5	5	5	5	5	5	5	5	5
Total weight	250	250	250	250	250	250	250	250	250

Table 7: Valsartan fast disintegration tablets formulations using various kinds & concentrations of super-disintegrants [32]

Ingredient (mg/tab)	**S1**	**S2**	**S3**	**S4**	**S5**	**S6**	**S7**	**S8**	**S9**	**S10**	**S11**	**S12**
Valsartan	40.0	40.0	40.0	40.0	40.0	40.0	40.0	40.0	40.0	40.0	40.0	40.0
HPMC	40.0	40.0	40.0	40.0	40.0	40.0	-	-	-	-	-	-
Gelatin	-	-	-	-	-	-	1.0	1.0	1.0	1.0	1.0	1.0
Crospovidone	2.0 1.0%	5.0 2.5%	10.0 5.0%	-	-	-	2.0 1.0%	5.0 2.5%	10.0 5.0%	-	-	-
SSG	-	-	-	2.0-1.0%	5.0-2.5%	10.0-5.0%	-	-	-	2.0-1.0%	5.0-2.5%	10.0-5.0%
Magnesium stearate	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0
Mannitol	152.0	149.0	144.0	152.0	149.0	144.0	155.0	152.0	147.0	155.0	152.0	147.0

CONCLUSION

Telmisartan formulations demonstrates that solid dispersion (TS5) and fast dissolving pellet formulation (TP3), both the techniques showed better drug release profile than MCC pellet and SMEDDS techniques. However, when it comes to dissolution rate, fast dissolving pellet In addition to that, a formulation optimized by factorial design as well as fast dissolving tablet (FDT) formulation signifies more conventional approach as well as good drug release profile. Formulation reflects notably best results among all. Furthermore, Valsartan formulation techniques evaluation leads us to conclude that liquisolid method showed good release profile as compare to conventional products but the method incorporates some complex requirements of load factor calculation and saturation solubility studies.

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