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FORMULATION AND EVALUATION OF TELMISARTAN TABLETS EMPLOYING SOLVENT DEPOSITED SYSTEMS

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ABSTRACT

Telmisartan, a widely prescribed anti-hypertensive drug belongs to class II under BCS classification and exhibit low and variable oral bioavailability due to its poor aqueous solubility. Because of poor aqueous solubility and dissolution rate it poses challenging problems in its tablet formulation development. The objective of the present study is to enhance the dissolution rate and dissolution efficiency of Telmisartan, a BCS class II drug by using solvent deposited systems. Solvent deposited systems of telmisartan in 1:5 drug: carrier ratio were prepared by solvent evaporation method. Telmisartan (40 mg) tablets were prepared employing its solvent deposited systems by direct compression method. All tablets prepared by employing solvent deposited systems fulfilled the official (IP2014) disintegration time specification of uncoated tablets. The correlation coefficient (r) values were higher in the first order model than in zero order model indicating that the dissolution of Telmisartan followed first order kinetics. Telmisartan dissolution was very rapid from the tablets formulated employing solvent deposited systems when compared to those formulated using telmisartan pure drug (F_1). All the dissolution parameters (PD_{10}, DE_{30}, and K_1) indicated rapid dissolution of telmisartan from tablets prepared by using solvent deposited systems. All the dissolution parameters ($PD_{10,}$ $DE_{30,}$ and $K_{1)}$ indicated rapid dissolution of Telmisartan from tablets prepared by employing solvent deposited systems. The order of increasing dissolution rate ($K_{1)}$ of Telmisartan observed with various tablet formulations was F4 > F6 > F5 > F_3 > F_2 > F_1.. All the tablets except formulation F1 fulfilled the official dissolution requirement of NLT 75% drug dissolution in 30 min (IP 2014). Telmisartan tablets containing Solvent deposited systems of Pearlitol Flash (F4) gave higher dissolution rate ($K_{1)}$ of Telmisartan

when compared with other formulations. Hence solvent deposited systems of Telmisartan in Pearlitol Flash is recommended for formulation of Telmisartan tablets with fast dissolution characteristics

KEYWORDS: Solvent Deposited Systems, Telmisartan, Dissolution Rate, Dissolution Efficiency.

INTRODUCTION

Telmisartan, a widely prescribed anti-hypertensive drug belongs to class II under BCS classification and exhibit low and variable oral bioavailability due to its poor aqueous solubility. Because of poor aqueous solubility in dissolution rate it poses challenging problems in its tablet formulation development. The poor dissolution characteristics of relatively insoluble drugs have long been a problem to the pharmaceutical industry. The solubility characteristic of a drug is a good indicator of gastrointestinal absorptivity. Poorly soluble drugs are characterized by low absorption and weak bioavailability. For such drugs, reduction of particle size generally increases the dissolution rate and hence improves the absorption and bioavailability. Among the various approaches to improve the dissolution of poorly soluble drugs, the solvent deposition technique (SDS) has proven to be very successful.[1-8] In this method the rate of dissolution is increased by depositing drug in minuscular form on the surface of an adsorbent. Minuscular form implies the molecularly micronized form of drug, when it is extensively dispersed on the extensive surface of the micro particulate adsorbents. During dissolution the minuscular drug system releases only free, absorbable drug into solution. The minuscular drug delivery system can be regarded as drug in a micro particulate form molecularly dispersed on the very extensive surface of carrier. The decrease in particle size and the resulting increase in surface area serve to increase the thermodynamic activity of the drug in the dispersed state which greatly enhances the rate of solution of the drug. The solvent deposition system is usually prepared by simple evaporation of the solvent used for distribution of the drug on the matrix.[9-11] The objective of the present study is to enhance the dissolution rate and dissolution efficiency of Telmisartan, a BCS class II drug by employing solvent deposited systems.

EXPERIMENTAL

Materials

Telmisartan was a gift sample from M/s Aurobindo Pvt. Ltd., Hyderabad. Spray Dried Lactose (SDL), Micricellac, Paerlitol Flash, Primojel, Microcrsytalline Cellulose (MCC), talc

and magnesium stearate were procured from commercial sources. All other materials used were of pharmacopoeial grade.

METHODS

Estimation of Telmisartan

An UV Spectrophotometric method based on the measurement of absorbance at 296nm in phosphate buffer of pH 7.5 was used for the estimation of Telmisartan. The method was validated for linearity, accuracy and precision. The method obeyed Beer's law in the concentration range of 1 – 10 µg/ ml. When a standard drug solution was repeatedly assayed (n=6), the relative error and coefficient of variance were found to be 0.7% and 1.10% respectively.

Preparation of solvent deposited systems in various carriers

Solvent deposited systems of telmisartan in 1:5 drug: carrier ratio were prepared by solvent evaporation method. The required quantity of telmisartan was dissolved in methanol (10ml) to get a clear solution in a dry mortar. Carriers were added to the drug solution in the mortar and mixed. The mixture was triturated continuously for 20min to evaporate the solvent. Trituration was continued until a dry mass was obtained. The mass obtained was further dried at 50^0 C for 1 h in hot air oven. The dried product was powdered and passed through mesh no 100 in each case.

Preparation of telmisartan Tablets by Direct Compression Method

Telmisartan (40mg) tablets were prepared employing its solvent deposited systems by direct compression method as per the formulae given in Table 2. Solvent deposited systems of telmisartan various carriers as per formula were initially prepared as described above. The dried solvent deposited systems, talc and magnesium stearate were passed through mesh no.80 and collected on to the bed of MCC and mixed. The tablet compositions were blended thoroughly in a closed polyethylene bag and directly compressed in to tablets using an 8-station Cadmach tablet punching machine employing 9mm flat punches.

Evaluation of Tablets

Telmisartan tablets prepared were evaluated for drug content, hardness, friability, disintegration time and dissolution rate as per official methods.

Hardness

The hardness of prepared tablets was determined by using Monsanto hardness tester and measured in terms of kg/cm^2.

Friability

The friability of the tablets was measured in a Roche friabilator using the formula

Friability = [(Initial weight- Final weight) / (Initial weight)] x 100%

Drug Content

Weighed tablets (5) were powdered using a glass mortar and pestle. An accurately weighed quantity of powder equivalent to 20 mg of telmisartan was taken into 25ml volumetric flask, methanol was added to dissolve the drug and the solution was made upto 25ml with methanol. The solution was suitably diluted with phosphate buffer of pH 7.5 and assayed for telmisartan at 296nm.

Disintegration time

Disintegration time of the tablets was determined using single unit disintegration test apparatus (Make: Paramount) employing water as test fluid.

Dissolution Rate Study

Dissolution rate of telmisartan tablets prepared was studied in phosphate buffer of pH 7.5 (900ml) employing eight station dissolution rate test apparatus (LABINDIA, DS 8000) using paddle stirrer at 50rpm and at a temperature of 37°C ± 1°C. One tablet was used in each test. Samples of dissolution fluid (5ml) were withdrawn through a filter at different time intervals and assayed for telmisartan at 296 nm. The sample of dissolution fluid withdrawn at each time was replaced with fresh drug free dissolution fluid and a suitable correction was made for the amount of drug present in the samples withdrawn. Each dissolution experiment was run in triplicate (n=3).

Analysis of Data

The dissolution data were analysed as per zero order and first order kinetic models. Dissolution efficiency (DE_{30}) values were estimated as suggested by Khan.[8]

Table No 1: **Formulae of Various Solvent Deposited Systems of Telmisartan Prepared.**

S.NO	Composition of Solid Dispersion	CODE

	(Drug: Carrier)	
1.	Telmisartan pure drug	F1
2.	Telmisartan: SDL (1: 5)	F2
3.	Telmisartan: Cellactose (1:5)	F3
4.	Telmisartan: Pearlitol Flash (1:5)	F4
5.	Telmisartan: Primojel (1:5)	F5
6.	Telmisartan: MCC (1:5)	F6

Table No 2: Formulae of Telmisartan Tablets Prepared.

Ingredient (mg/tab)	F_1	F_2	F_3	F_4	F_5	F_6
Telmisartan	40	-	-	-	-	-
Telmisartan (solvent deposited systems)	-	240	240	240	240	240
Crospovidone	15	15	15	15	15	15
PVP K30	6	6	6	6	6	6
Talc	6	6	6	6	6	6
Magnesium stearate	6	6	6	6	6	6
MCC	227	27	27	27	27	27
Total weight (mg)	300	300	300	300	300	300

Table No 3: Flow Properties of Telmisartan Tablet Powder Blends Prepared using Solvent deposited Systems.

Formulation	Angle of repose (θ) ($\bar{x}$±SD)	Compressibility Index (%) ($\bar{x}$±SD)
F_1	17.46 ± 0.22	10.56 ± 0.21
F_2	18.47 ± 0.33	10.23 ± 0.19
F_3	21.32 ± 0.39	11.56 ± 0.14
F_4	20.43 ± 0.25	11.89 ± 0.18
F_5	18.90 ± 0.32	10.47 ± 0.14
F_6	21.72 ± 0.24	11.82 ± 0.09

Table No 4: Physical Parameters of Telmisartan Tablets.

Formulation	Hardness (Kg/cm^2)	Friability (% Wt loss)	Disintegration Time (min-sec)	Drug Content (mg/tablet)
F_1	4.5	0.75	2-20	39.4
F_2	4.5	0.65	1-30	39.2
F_3	5.0	0.52	1-40	40.6
F_4	5.0	0.82	0-50	40.1
F_5	4.5	0.73	1-20	40.3
F_6	5.0	0.68	1-00	39.4
Telma 40	4.5	0.80	2-18	40.6

Table No 5: Dissolution Parameters of Telmisartan Tablets.

Formulation	PD_{10} (%)	DE_{20} (%)	K_1 (min^{-1})	Official Dissolution

				Rate Test Specification
F_1	35.55 ± 0.51	28.85 ±0.23	0.0182	NLT 75% in 30 min (IP 2014)
F_2	70.77 ± 1.18	63.56 ±1.14	0.0895	
F_3	85.71 ± 1.33	66.73±1.25	0.106	
F_4	95.26 ± 1.65	84.06±1.45	0.304	
F_5	79.92 ± 0.59	72.039 ±1.37	0.160	
F_6	92.26 ± 0.59	81.87 ±1.24	0.255	
Telmikind	61.06 ±0.78	76.47± 1.21	0.124	

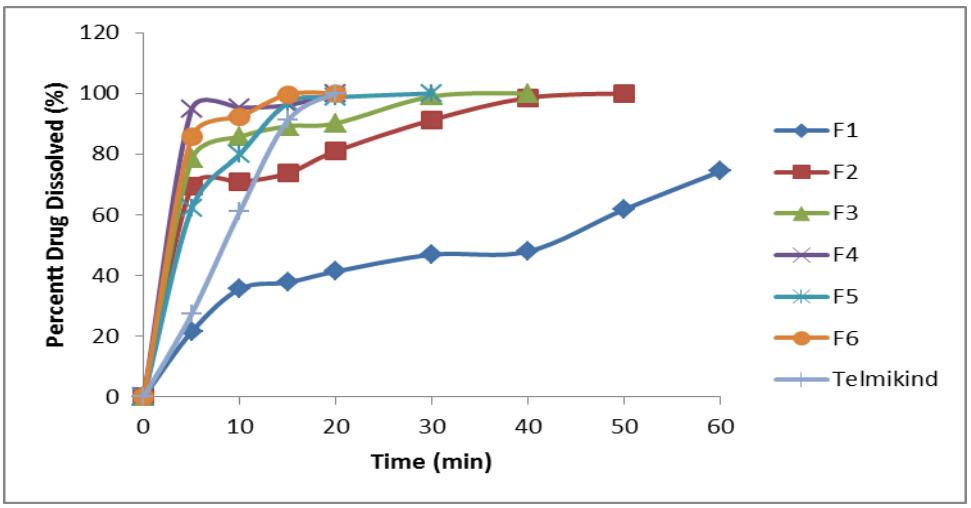

Fig No 1: Dissolution Profiles of Telmisartan Tablets Prepared employing various solvent deposited systems.

DISCUSSION OF RESULTS

The objective of the present study is to enhance the dissolution rate and dissolution efficiency of Telmisartan, a BCS class II drug by employing solvent deposited systems.

An U.V Spectrophotometric method based on the measurement of absorbance at 296nm in phosphate buffer of pH 7.5 was used for estimation of telmisartan. A calibration curve was constructed and the method was validated for linearity, accuracy, precision and interference. The method obeyed Beer's law in the concentration range of 0-10µg/ml. Low RSD values (1.71%) ensured reproducibility of the method. When a standard drug solution was repeatedly assayed (n=5) the relative error and coefficient of variation were found to be 0.45% and 1.65% respectively. Thus the method was found to be suitable for the estimation of telmisartan contents in various products and *in vitro* dissolution rate studies.

Solvent deposited systems of Telmisartan in various carriers (1:5 ratio of drug: carrier) were prepared by solvent evaporation method. All the solvent deposited systems prepared were found to be fine and free flowing powders. These solvent deposited systems were compressed

into tablets by direct compression. Powder blends were evaluated for flow properties and values are given in Table 3. The results indicated that the powder blends were found suitable for direct compression because of their good flow properties. Tablets each containing 40 mg of Telmisartan were formulated and were evaluated for evaluated for drug content, hardness, friability, disintegration time and dissolution rate characteristics.

The physical parameters of the Telmisartan tablets prepared are given in Table 4. The hardness of the tablets was in the range 4.5-5.0 kg/cm^2. Weight loss in the friability test was less than 0.82% in all the cases. Telmisartan content of the tablets prepared was within 100±3 %. All the tablets disintegrated within 3 min. All tablets prepared by both the methods fulfilled the official (IP2014) disintegration time specification of uncoated tablets.

The dissolution rate of various Telmisartan tablets prepared was studied in phosphate buffer of pH 7.5 as prescribed in IP 2014. The dissolution profiles of various tablets prepared are shown in Fig 1 and dissolution parameters of Telmisartan tablets prepared are given in Table 5.

The dissolution data were analyzed as per zero order and first order kinetics in each case. The correlation coefficient (r) values were higher in the first order model than in zero order model indicating that the dissolution of Telmisartan followed first order kinetics. The correlation coefficient (r) values in the first order model were found to be in the range of 0.920-0.985. The corresponding first order dissolution rate (K_1) values of various products were estimated from the slope of the first order linear regressions. Dissolution Efficiency (DE_{30}) values were calculated as described by Khan.[12]

Telmisartan dissolution was very rapid from the tablets formulated employing solvent deposited systems when compared to those formulated using Telmisartan pure drug. All the dissolution parameters (PD_{10}, DE_{30}, and K_1) indicated rapid dissolution of Telmisartan from tablets prepared by employing solvent deposited systems. All the tablets except formulation F1 fulfilled the official dissolution requirement of NLT 75% drug dissolution in 30 min (IP 2014). The order of dissolution rate (K_1) of Telmisartan observed with various tablet formulations was F4 > F6 > F5 > F_3 > F_2 > F_1. Telmisartan tablets containing Solvent deposited systems of Pearlitol Flash (F4) gave higher dissolution rate (K1) of Telmisartan when compared with other formulations and commercial tablet.

CONCLUSIONS

From the results obtained the following conclusions are drawn:

1. All tablets prepared by employing solvent deposited systems fulfilled the official (IP2014) disintegration time specification of uncoated tablets.
2. The correlation coefficient (r) values were higher in the first order model than in zero order model indicating that the dissolution of Telmisartan followed first order kinetics.
3. Telmisartan dissolution was very rapid from the tablets formulated employing solvent deposited systems when compared to those formulated using telmisartan pure drug (F_1).
4. All the dissolution parameters (PD_{10}, DE_{30}, and K_1) indicated rapid dissolution of telmisartan from tablets prepared by using solvent deposited systems.
5. The order of dissolution rate ($K_{1)}$ of Telmisartan observed with various tablet formulations was F4 > F6 > F5 > F_3 > F_2 > F_1.
6. All the tablets except formulation F1 fulfilled the official dissolution requirement of NLT 75% drug dissolution in 30 min (IP 2014).
7. Telmisartan tablets containing Solvent deposited systems of Pearlitol Flash (F4) gave higher dissolution rate ($K_{1)}$ of Telmisartan when compared with other formulations and commercial tablet.
8. Hence solvent deposited systems of Telmisartan in Pearlitol Flash is recommended for formulation of Telmisartan tablets with fast dissolution characteristics

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