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FORMULATION OF CRYSTALLO-CO-AGGLOMERATES OF TELMISARTAN: STUDY OF EFFECT OF POLYMERS ON DRUG RELEASE

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ABSTRACT

The present work is aimed to formulate spherical agglomerates of telmisartan by crystallo-co-agglomeration technique and enhance the micromeritic properties, solubility and dissolution rate of telmisartan, a poorly water soluble anti-hypertensive drug. Chloroform-water system containing PEG 6000 & HPMC in different concentration was used as the crystallization medium. Chloroform act as good solvent and bridging liquid for telmisartan and water as bad solvent. The agglomerates were characterized to various physicochemical evaluations such as practical yield, drug content, particle size, FTIR spectroscopy, scanning electron microscopy, micromeritic properties and solubility analysis. The dissolution studies were carried out using PBS of pH 7.4 as dissolution media maintained at 37.5°C for 70 minutes. The dissolution data demonstrate that the rate of drug release is dependent upon the nature and concentration of polymer used in the formulation. Formulation TP2 (combination of telmisartan and PEG 6000) in the ratio 1:1.5 was selected as an optimum formulation which showed better results with respect to drug release, solubility and micromeritics when compared to other formulation.

Key Words: Telmisartan, Crystallo-co-agglomerates, PEG6000, HPMC.

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INTRODUCTION

Among all the routes explored for systemic delivery of drugs, oral drug delivery has been known for decades as the most widely used route for drug administration. It is also a well established fact that the oral route of drug administration have wide acceptance up to 50-60% of total dosage forms. The reason that the oral route achieved such popularity may be in part attributed to its ease of administration, cost effectiveness as well as better patient compliance [1]. Today the tablet is the most popular dosage form of all pharmaceutical preparations produced. From the manufacturing point of view tablets can be produced at much higher rate than any other dosage form. The material used for the production of tablet should be in physical form that flows smoothly, directly compressible and physically stable so as to achieve rapid production capability of tablet formulation.

There are various methods for tablet preparation out of which direct compression is the most efficient process used in tablet manufacturing because it is the fastest, simplest and least expensive tablet-compression procedure. Many processing steps mainly granulation and drying are omitted in direct compression, and additionally, wet technology cannot be used with sensitive agent (e.g., in effervescent tablet making). Direct tableting of pharmaceutical materials is desirable to reduce the cost of production. However, compressing a drug directly requires good micromeritic properties, such as flowability, and a good and reproducible compression behavior. To impart these properties the drugs are subjected to particle design techniques, spherical crystallization is one the techniques of particle design.[2]

In the pharmaceutical field, Kawashima et al. have given impulse to the research of the spherical crystallization process. "Spherical crystallization" was defined by Kawashima as "an agglomeration technique that transforms crystals directly into a compacted spherical form during the crystallization process."[3] Spherical crystallization is a particle design technique which is restricted to only water insoluble single large dose drugs only because several excipients are hydrophilic in nature hence addition of these excipients in the agglomerates with help of organic bridging liquid is difficult. Kadam et al developed the crystallo-co-agglomeration (CCA) technique, which is a modification of spherical crystallization. CCA has been designed to overcome the limitations of spherical crystallization to obtain directly compressible agglomerates.[4] The process of CCA involves simultaneous crystallization and agglomeration of drug/s with/without excipients from good solvent and/or bridging liquid by addition of a non-solvent. This technique is simple, less expensive, may be an advantages for developing it on a commercial scale for manufacturing of tablets

Telmisartan is a BCS class II drug. Telmisartan is having poor aqueous solubility. The poor water solubility and poor micromeritic properties of Telmisartan lead to low dissolution rate and poor flow during tableting. In this study, novel spherical agglomeration technique called Crystallo-co-agglomeration(CCA) is used for the solubility enhancement and cost effective production of Telmisartan was carried out in the presence of hydrophilic polymers such as HPMC and PEG 6000.

The aim of this study was to improve the bioavailability of Telmisartan by crystallo coagglomerates and to investigate the micromeritic and dissolution properties of Telmisartan agglomerates in presence of above mentioned polymers.

MATERIALS AND METHOD

Materials

Telmisartan was obtained from Yarrow chem. Products Ltd, India. HPMC was procured from ARA fine chemicals. PEG 6000 from Balaji chemicals Gujrath, Choroform was procured from nice chemicals pvt ltd, India. All other chemicals and reagents used were of analytical grade.

Methodology

Preparation of standard graph [5]

The standard stock solutions were scanned at wavelengths between 200 nm and 400 nm for the determination of λ_{max}. The λ_{max} for TELMISARTAN were found to be 294 nm. From the standard stock solution a series of dilutions were made using PBS pH 7.4 solution. The absorbance of these solutions was measured against a blank of PBS pH 7.4 solutions in UV/Visible spectrophotometer at 294 nm. Standard graphs were then plotted.

Determination of drug- polymer incompatability by Fourier Transform Infrared (FT-IR) spectroscopy

FTIR spectral analysis of pure drug and polymer was carried out individually and also in different ratio, observation was made whether changes in the chemical constitution of drug after combining it with the polymer occurred. The absorption maximums in spectrum were compared with the reference spectrum.

Formulation of Crystallo CO Agglomerates [1]

Seven formulations were prepared using different polymer solutions (PEG 6000 and HPMC) in different concentrations (Table-1). The drug was dissolved in Chloroform and portion of the total amount of available talc. This solution was then slowly added to a solution of the polymer in distilled water and talc, which was stirred using a mechanical stirrer for 20 minutes at 800 rpm, to form the spherical crystals.

The spherical crystals formed were then filtered, washed with water and air-dried. Separate one formulation was developed without using any polymer ie, talc and drug only (blank).

Table 1: Composition of developed formulations

INGREDIENTS	Formulation code						
	T01	**TP1**	**TP2**	**TP3**	**TH1**	**TH2**	**TH3**
Telmisartan(g)	0.040	0.040	0.040	0.040	0.040	0.040	0.040
PEG 6000(g)	-	0.100	0.200	0.300	-	-	-
HPMC(g)	-	-	-		0.100	0.200	0.300
Talc(g)	0.200	0.200	0.200	0.200	0.200	0.200	0.200
Chloroform(ml)	13	13	13	13	13	13	13
Distilled water	qs	qs	qs	qs	qs	qs	qs

Evaluation of Crystallo CO Agglomerates [6]

Particle shape and surface morphology

Particle shape and surface morphology of agglomerates were determined by Scanning Electron Microscopy.

Yield of crystallo co agglomerates

The prepared agglomerates were collected and weighed. The measured weight was divided by the total amount of all non-volatile compounds which were used for preparation.

Drug content

50 mg of agglomerates was weighed and dissolved in 10ml methanol and was diluted to 100ml with PBS pH 7.4 Absorbance of the resulting solution was measured at 294 nm. Drug content was determined from standard plot.

Solubility Analysis[7]

The solubility of developed spherical agglomerates in distilled water was determined by taking excess quantity of spherical agglomerates and added to screw capped 50 ml glass vials. The vials were shaken for two hours using mechanical shaker. The solution was filtered. The drug concentration was determined UV spectrophotometrically at 294 nm .

Micromeritic Property[8]

a) Bulk Density

The bulk density was calculated using the formula**.**

$$\rho b = \frac{M}{Vb}$$

b) Tapped Density

The tapped density (ρt) was calculated using the formula.

$$\rho t = \frac{M}{Vt}$$

c) Compressibility Index

Compressibility index (C.I) which is calculated as follows

$$C.I = \frac{(\rho t - \rho b)}{Pt} \times 100$$

d) Hausner Ratio

Hausner ratio (Hr) is an indirect index of ease of powder flow. It is calculated by the following formula

$$Hr = \frac{\rho t}{Pb}$$

e) Angle of Repose

Angle of repose was determined using funnel method. Angle of repose (θ) was calculated using the formula.

$$\tan \theta = \frac{h}{r}$$

***In-vitro* dissolution studies**

A quantity of Crystallo-co-agglomerates equivalent to 40mg of Telmisartan was placed in the basket of USP type I (Basket) *in vitro* dissolution apparatus at 75 rpm in 900ml of PBS of pH 7.4 as dissolution media maintained at 37.5°C. Aliquot of 5ml was withdrawn at specified time interval (0, 10, 20, 30, 40, 50, 60 and 70min). All aliquots were filtered and analyzed UV-spectrophotometrically at 294nm. Each withdrawal was replaced with fresh dissolution medium to maintain a constant volume throughout the test.

Stability study

Accelerated stability studies were performed on best formulation by using ICH guidelines. With necessary modification. Sample was stored at condition of 40±2°C and 75%±5% RH for a period of 45 days. After the period of 45 days sample was tested for drug content and angle of repose.

RESULTS AND DISCUSSION

Calibration curve for Telmisartan in PBS of pH 7.4

Standard solutions of Telmisartan in different concentrations were prepared using PBS of pH 7.4 and their absorbance was measured at 294 nm. Drug concentration against absorbance was plotted (fig-1). Regression coefficient & slope was found to be 0.99 & 0.067 respectively. The calibration curve was found to be linear in concentration range of 2-10µg/ml. Hence Beer-Lambert's law is obeyed

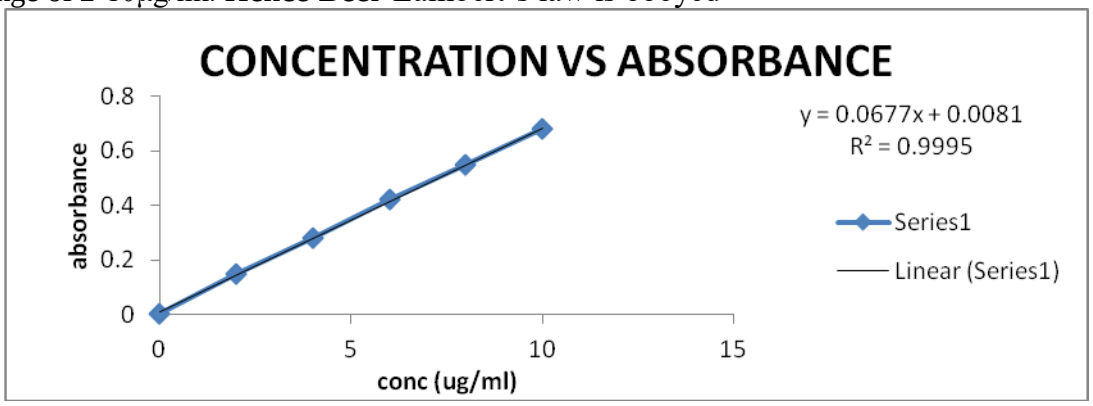


Fig-1: Calibration curve of telmisartan in pbs at pH 7.4

Drug- Polymer Incompatability by Fourier Transform Infrared (FT-IR) Spectroscopy

Infrared spectrum of pure Telmisartan is shown in fig 2. The characteristic absorption peak was obtained at 1599 cm^{-1}due to C=N, 839 cm^{-1} due to C-N, 3749 cm^{-1} due to aromatic C-H stretch, 1697 cm^{-1} due to C=C bonding, 3702 cm^{-1}due to O-H stretch.

By comparing the FTIR spectrum of Telmisartan with drug-polymer agglomerates fig 2 it was concluded that all the characteristic absorption bands of Telmisartan were retained, hence there was no chemical interaction between Telmisartan and hydrophilic carriers.

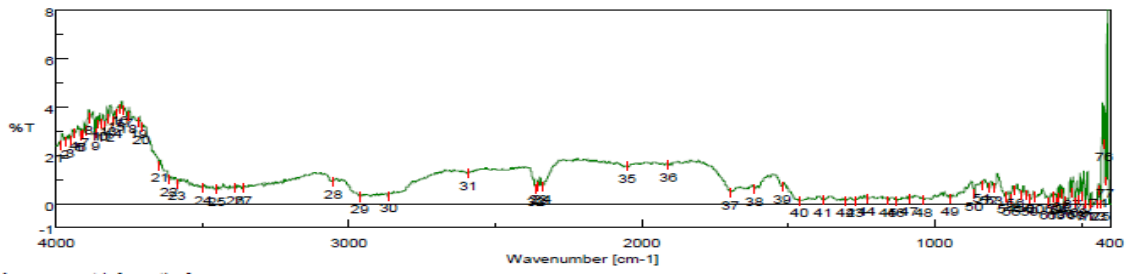


Fig-2 FT-IR Spectrum of Telmisartan +PEG 6000+HPMC

Formulation of crystallo co agglomerates

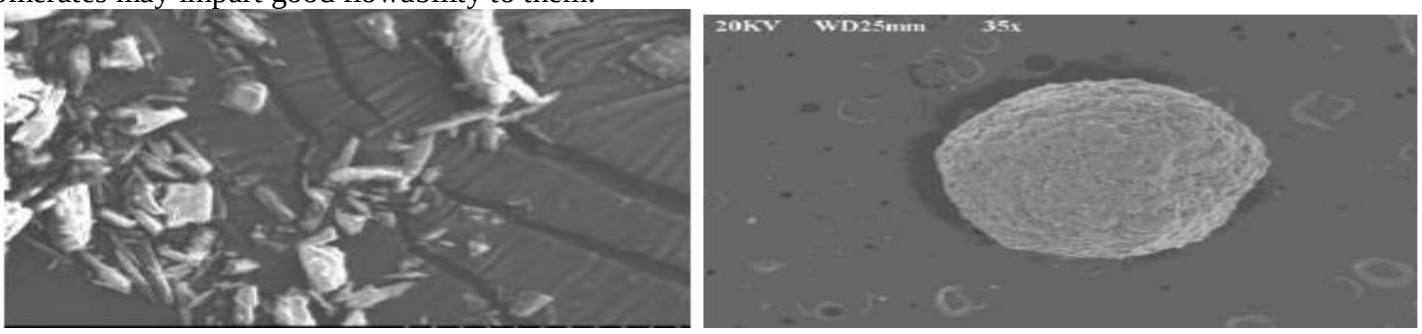
Spherical agglomerates of Telmisartan was prepared by crystallo co agglomeration technique using a three solvent system such as good solvent, poor solvent and bridging liquid. Here good solvent and bridging liquid were same which was chloroform. Water was used as the poor solvent. The selection of these solvents depends on the miscibility of the solvents and the solubility of drug in individual solvents. A solution of the drug in the good solvent (chloroform) was added to the poor solvent (water), which contained the polymers to be used such as PEG 6000 and HPMC at different concentrations. For increasing bulkiness talc may be added to it. On addition of the drug solution to the polymer solution, the drug crystals precipitate out, resulting in formation of spherical agglomerates.

The speed of agitation was kept constant at 800 rpm. It was found that at lower speeds, the agglomerates formed were irregular and large. When stirred at a faster rate, the agglomerates were very small in size. Developed formulations were packed and stored at room temperature and used for further evaluations

Evaluation of developed spherical agglomerates

Particle shape and surface morphology

The SEM photographs of pure Telmisartan and the formulation which gave the smoothest sphere was given in Fig-3. This proves that needle-like, fine crystals of Telmisartan may be effectively converted to compact spherical agglomerates by the process of crystallo co agglomeration. The smooth surface and spherical shape of the agglomerates may impart good flowability to them.



(i) (ii)

Fig-3 Spherical agglomerates of pure Telmisartan (i) and cca of Telmisartan

Yield of spherical agglomerate and Drug content estimation

The percentage yield is estimated for the formulations were between 94.57%±0.59 to 71.25%±0.73 %. % Drug content of all the formulation (agglomerates) varied from 90.85% to 96.55% as shown in table-2. This showed that there was uniform distribution of drug throughout the batch**.**

Solubility analysis

The result for solubility studies for pure Telmisartan and agglomerates were shown in table-2. The solubility of pure Telmisartan was determined as (0.58±0.01mg/ 100 ml).Solubility of Telmisartan agglomerates prepared were in the range of 0.83±0.02-1.34±0.08 mg/ 100 ml. Solubility of all developed formulations was far superior than the pure Telmisartan TP2, showing highest solubility of 1.34±0.08 mg/ 100 ml.

Table-2: %yield, % Drug content and solubility of pure telmisartan and drug-polmer Agglomerates

Formulation Code	%Yield	%Drug content	Solubility(mg/100mL)
TEL			0.58±0.01
T01	90.68%±0.92	78.05%±0.66	0.83±0.02
TP1	94.57%±0.59	92.36%±1.23	1.12±0.04
TP2	85.48%±0.46	95.02%±0.45	1.34±0.08
TP3	79.54%±0.76	96.55%±1.26	0.97±0.05
TH1	93.87%±0.94	93.23%±.0.54	0.91±0.03
TH2	82.65%±0.78	92.98%±0.45	0.92±0.06
TH3	71.25%±0.73	90.85%±0.37	0.94±0.09

Micromeritic properties

The results for micromeritic propertiesnof pure drug and agglomerates were shown in Table- 3. From the results of micromeritic studies it can be concluded that the agglomerates showed improvement in flow property when compared to pure Telmisartan.

Among the different agglomerates prepared, formulation TP2 showed maximum flowability as evident by low values of angle of repose (14.2 ± 0.87^0), Hausner's ratio (1.06) and Carr's index (5.13%).

Table-3: Micromeritics of pure drug and agglomerates

Formulations	Bulk density gm/cm^3	Tapped density gm/cm^3	Carr's index (%)	Hausner's ratio	Angle of Repose (^{o})
TEL	0.24±0.02	0.44±0.03	46.6	1.69	32±0.90
T01	0.30±0.04	0.47±0.08	14.19	1.18	19.8±0.67
TP1	0.45±0.04	0.50±0.08	5.71	1.07	16.2±0.94
TP2	0.49±0.03	0.53±0.04	5.13	1.06	14.2±0.87
TP3	0.42±0.05	0.49±0.12	7.95	1.10	18.1±0.79
TH1	0.41±0.06	0.48±0.06	16.6	1.20	16.7±0.67
TH2	0.46±0.09	0.51±0.02	11.89	1.15	17.6±0.34
TH3	0.40±0.08	0.49±0.09	14.61	1.18	14.3±0.56

***In-vitro* Dissolution study**

In-vitro dissolution studies for drug telmisartan and prepared CCAs were carried out. When % drug release was assessed, the formulation TP1 was able to release 73.47±0.97% of Telmisartan IP from the developed spherical agglomerates. Whereas TP2 and TP3 had 79.82±0.22% and 71.69±0.22% of drug release at the end of 70 minutes study period. The three formulations had almost similar drug release profile, but may be TP2 with its 0.200g PEG 6000 was showing better and maximum release of Telmisartan IP during 70 minutes study period (Table-4). Similarly TH2 was showing the drug release of (72.11±0.70%). TH3 formulated with Drug: Polymer in 1:7.5 proportion showed a release less than that of TH1 which was formulated with Drug: Polymer in 1:2.5proportion. The concentration of polmer may be a factor to be considered during the development of spherical agglomerates containing drug. At higher concentration of polymer, it may be attributed to deposit more on the drug surface which may result in reduced drug release from the developed spherical agglomerates of drug. Low concentration retards the release as it poorly trigger wetting.

Table-4 *In vitro* dissolution profile of drug-polymer agglomerates

TIME (min)	%drug release					
	TP1	TP2	TP3	TH1	TH2	TH3
0	0	0	0	0	0	0
10	22.87±1.17	25.56±0.80	22.35±0.47	14.30±1.47	15.98±0.94	14.86±1.9
20	34.65±0.47	38.60±0.79	32.98±0.78	21.36±0.97	22.01±1.47	20.98±0.90
30	42.60±0.46	48.44±0.46	39.60±0.56	32.55±0.76	33.64±1.45	32.69±0.55
40	49.46±0.94	56.88±0.23	47.70±0.34	44.55±0.34	45.22±0.99	43.90±0.67
50	55.71±0.65	60.23±0.71	52.68±0.67	52.36±0.25	53.57±0.83	50.91±0.45
60	69.56±0.98	72.11±0.24	62.54±0.34	60.99±0.46	66.24±0.71	58.46±0.76
70	73.47±0.97	79.82±0.22	71.69±0.22	69.5±0.78	72.11±0.70	66.46±0.56

According to these findings, spherical agglomerates with polymer concentration of 0.200 g were found to be suitable for the maximum drug release. So formulations TP2 and TH2 were selected for further assessment. Simultaneously they are compared with % release of formulation without polymer (T01) (Table-5).

Table-5 Comparison of % drug release from spherical agglomerate

TIME (min)	%drug release		
	T01	TP2	TH2
0	0	0	0
10	10.35±0.90	25.56±0.80	15.98±0.94
20	18.39±0.78	38.60±0.79	22.01±1.47
30	23.37±0.56	48.44±0.46	33.64±1.45
40	32.69±0.79	56.88±0.23	45.22±0.99
50	47.62±0.56	60.23±0.71	53.57±0.83
60	55.54±0.78	72.11±0.24	66.24±0.71
70	62.65±0.99	79.82±0.22	72.11±0.70

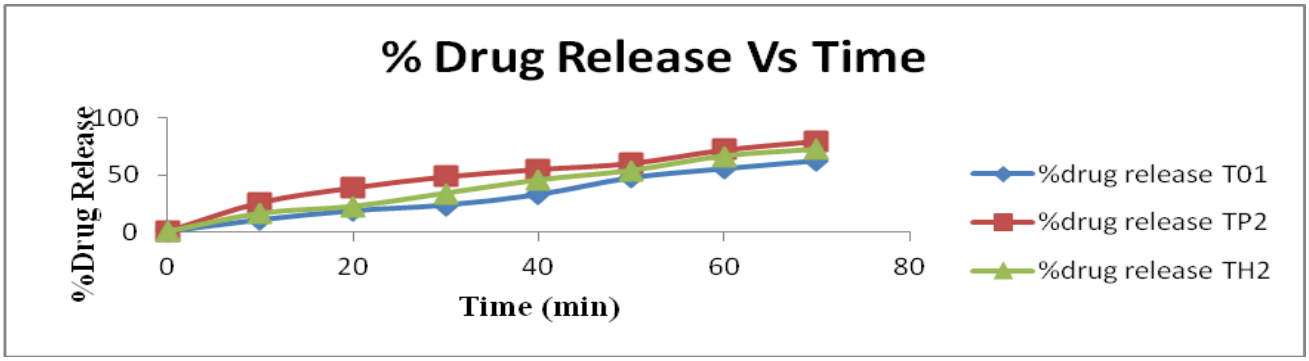


Fig-4 Comparison of % drug release from spherical agglomerate

Formulation TP2 with PEG 6000 showed impressive profile with high percentage of drug release ie, 79.82±0.22% at the end of 70 minutes. Formulations TH2 and T01 showed 72.11±0.70% and 62.65±0.99% drug release in PBS of pH 7.4 When these datas were compared the drug release profile was in the following order TP2> TH2>T01 Based on the evaluation data collected from % drug release, % yield, micromeritic properties and *in vitro* drug profile TP2 may be the best developed formulation. Hence TP2 may be selected and subjected for stability study (Fig-4)

Stability studies

The results of stability Accelerated stability in table shows no significant changes. Hence TP2 with optimum concentration of PEG 6000 was able to develop stable spherical agglomerates of Telmisartan (Table-6).

Table-6 Stability studies of TP2

Formulation code	Drug content		Angle of repose	
	After stability study	before stability study	After stability study	Before stability study
TP2	94.69±0.89	95.02%±0.45	15.12±0.98	14.2±0.87

COCLUSION

Telmisartan agglomerates were successfully prepared by CCA technique using hydrophilic polymers like PEG 6000 and HPMC. Agglomerates exhibited improved micromeritic properities compared to pure drug. Formulation, TP2 was selected as an optimized formulation which showed better results with respect to percent drug release, percent drug content and micromeritics properties. Hence this CCA technique can be used for formulation of tablet of Telmisartan by direct compression with directly compressible tablet excipients.

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