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RESEARCH ARTICLE

Formulation and Evaluation of Directly Compressible Agglomerates of Telmisartan

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ABSTRACT:

The present work is aimed to formulate spherical agglomerates and enhance the micromeritic properties, solubility and dissolution rate of Telmisartan, a poorly water soluble anti-hypertensive drug. The poor water solubility and poor micromeritic properties of telmisartan lead to low dissolution rate and poor flow during tableting. Telmisartan spherical agglomerates were prepared by spherical agglomeration techniques using a quasi emulsion solvent diffusion method consisting of chloroform and water as good solvent and bad solvent respectively. PVP K30 and PEG 6000 in different concentration were used as hydrophilic polymers in agglomeration process. The effects of drug to excipient ratio, stirring time, temperature and stirring speed on the physical characteristics of agglomerates were investigated. The agglomerates were characterized to various physicochemical evaluations such as practical yield, drug content, particle size, IR spectroscopy, scanning electron microscopy, micromeritic properties, solubility and dissolution studies.Tablets were prepared using spherical agglomerates by direct compression and evaluated for tablet properties. Dissolution profiles of the directly compressed tablets of spherical agglomerates were compared with conventional tablets.

KEYWORDS: Telmisartan, Spherical agglomeration, Micromeritic properties, solubility and dissolution rate.

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.

Tablets represent the unit oral solid dosage form which has been in existence since the nineteenth century. They comprise a mixture of ingredients presented in a single entity, usually containing an accurate dose of a drug. Tablet is the major oral solid dosage form, having significant advantage over capsules because of its tamper proof nature. They also offer the greatest capabilities of all oral dosage forms for the greatest dose precision and least content variability. Other factors like low cost, compactness, easy packing and shipping, simple product identification, better patient compliance, achievement of desired release profile, better suitability to large scale production also adds to the potential popularity of the tablets among oral solid dosage forms.[1]

It is well known that most common methods for tablet manufacturing include dry granulation, wet granulation and direct compression. It has been reported that among all the tabletting techniques, direct compression is the simplest and cost effective method to produce tablets. It is economical, less stressful to ingredients in terms of heat and moisture and only few procedures are involved in it.[2] But most of the drugs cannot be directly compressed due to lack of their binding or bonding characteristics into the compact entities.[3] Hence, for direct compression of these drugs, either large amount of directly compressibly excipients are required to be included into the formulation which in turn proves costly or alteration of physicochemical properties of the drug by various particle engineering techniques are required to be done.

Several techniques which modify the physical properties of the drug substance *viz* particle engineering are:[4]

(1) Extrusion Spheronozation
(2) Spray Drying
(3) Melt Sono Crystallization
(4) Co-crystallization
(5) Melt Solidification
(6) Spherical Agglomeration
(7) Crystallo-co-agglomeration etc.

Spherical Agglomeration

Spherical agglomeration (SA) is a novel particle engineering technique by which crystallization and agglomeration can be carried out simultaneously in one step to transform crystals directly into compacted spherical shape that helps to achieve good flowability and compressibility. The process involves simultaneous crystallization and agglomeration of drugs with or without excipients to obtain directly compressible blends.[5]

Compared to conventional granulation techniques which are slow and time consuming, SA technique employs a relatively fewer steps in the compression of tablets, reducing the cost of manufacturing.[6]

The typical spherical crystallization technique employs three solvents: one is the substance dissolution medium; another is a medium, which partially dissolves the substance, and third is the wetting solvent for the substance.[7]

Quasi Emulsion Solvent diffusion Method (QESD) [8]

In the QESD method the affinity between the drug and the good solvent is stronger than that of the good solvent and the poor solvent. Residual good solvents in droplets act as bridging liquid to agglomerate the generated crystals.[9] The drug is dissolved in the good solvent, and the solution is dispersed into the poor solvent, producing emulsion (quasi) droplets, even if the solvents are normally miscible. The good solvent diffuses gradually out of the emulsion droplets into the surrounding poor solvent phase, and the poor solvent diffuses into the droplets.

MATERIAL AND METHODS

MATERIALS

Telmisartan (drug) was provided by Healthbiotech India PVT. LTD and PEG 6000, PVP K30, Talc, Magnesium stearate was purchased from Rankem laboratory, Gurgaon, Haryana and other chemicals were purchased by local market, Bhopal.

METHOD OF PREPARATION

A solution of telmisartan in chloroform (1.0 g in 13 ml) was prepared. The agglomerates were obtained by adding the above solution drop wise into an aqueous phase water (100 ml) containing dissolved polymer at different concentration in room temperature. The mixture was stirred at 1000 rpm using a controlled speed stirrer for 30 minutes. Agglomerates were prepared using chloroform as a good solvent for telmisartan and water was used as a bad solvent. The agglomerates were also formulated using different polymers like PEG 6000 and PVP K30 in 4 different ratios of 1:1, 1:2, 1:3, and 1:4.

The agglomerates formed were then separated by filtration and dried at room temperature.

1. Then Agglomerates were lubricated with 1 % w/w talc and 1% w/w magnesium stearate.
2. The lubricated agglomerates were compressed into tablets using a compression machine.

Table 1- Formulation Of Different Batches

Ingredients	F1 (1:1)	F2 (1:2)	F3 (1:3)	F4 (1:4)	F5 (1:1)	F6 (1:2)	F7 (1:3)	F8 (1:4)
Telmisartan(g)	1	1	1	1	1	1	1	1
PEG 6000 (g)	1	2	3	4	-	-	-	-
PVP K30(g)	-	-	-	-	1	2	3	4

PREFORMULATION STUDIES[10]:

Preformulation testing is the first step in the rational development of dosage forms of a drug substance. Preformulation study was done initially and results were directed for the further course of formulation.

Table 2- Results of flow properties of Telmisartan

PARAMETER	VALUE
Bulk Density (gm/cm^3)	0.26±0.04
Tapped Density (gm/cm^3)	0.44±0.03
Hausner's ratio	1.69
Carr's Index (%)	40.9
Angle of repose	32^0

Organoleptic property[11]: The physical characteristic like organoleptic properties of drug sample was performed and it was found to be color was white off-crystalline powder and was odourless. And hence the drug sample was found to be as per specifications.

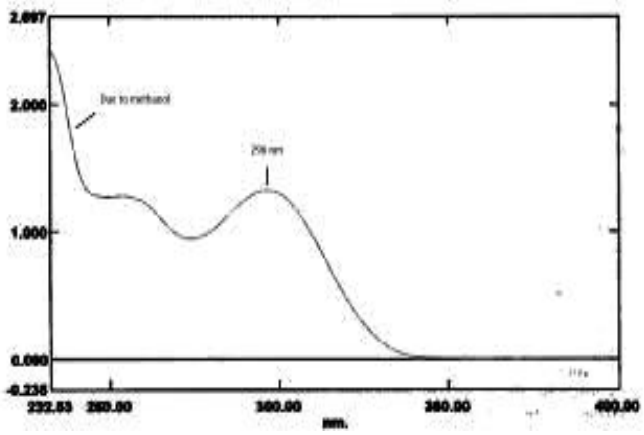
Solubility of Telmisartan[12]: The quantitative solubility of drug was determined and it was found that drug freely soluble in, chloroform and dichloromethane ,practically insoluble in water or an aqueous solution in the pH range of 3 to 9, sparingly soluble in strong acid and with the exception of hydrochloric acid in which it is insoluble.

Melting point determination[13]: Melting point of Telmisartan was determined by using melting point apparatus.

Table 3- Melting Point of telmisartan

Drug	Standard	Observation
Telmisartan	261-263^0 C	264-266ºC

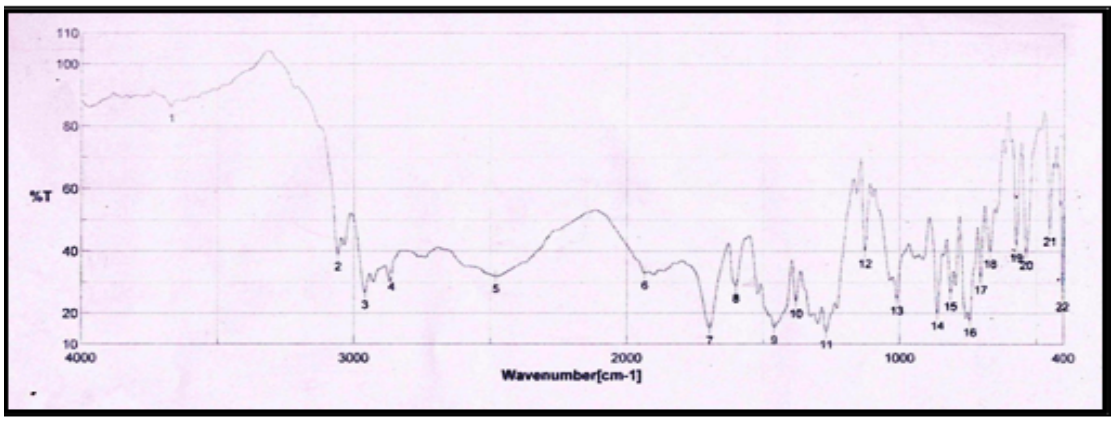
UV Spectroscopy: Identification and authentication of drug sample was done by ultraviolet spectroscopy and it was scanned in the range of 200-400 nm. Drug absorption maximum λ_{max} was found to be at 291 nm. Absorption maximum showed that drug sample was authenticated.



Graph –1: UV spectra of Telmisartan

IR Test sample

Telmisartan sample was confirmed by IR spectroscopy using bruker spectrometer, Japan. The characteristic peaks were compared with IR spectrum as given in pharmacopoeia.



Graph -2: FTIR Spectrum of Telmisartan

Hence On the basis of preformulation study the drug sample of Telmisartan was found pure and authenticated and the sample was used for the further preparation.

CHARACTERIZATION OF DOSAGE FORM[14]

Morphological study and Organoleptic properties:

Shape, surface and color of capsules are examined by naked eye.

Post compression parameters:

The properties of the tablets like thickness, hardness and friability, for the formulations F_1 to F_8 were determined and the results are reported in table. The results of weight variation[15] and in vitro disintegration[16] for the formulations F_1 to F_8, were determined and the results were reported as shown in table 4.

Table 4 - Results for Thickness, Hardness, Friability

Formulatios	Thickness (mm)	Hardness (Kg/cm^2)	Friability (%)
F_1	3.29±0.03	3.12±0.10	0.52±0.04
F_2	3.32±0.05	3.45±0.20	0.54±0.05
F_3	3.25±0.01	4.22±0.45	0.40±0.07
F_4	3.31±0.04	4.40±0.25	0.44±0.08
F_5	3.30±0.06	3.65±0.13	0.41±0.02
F_6	3.33±0.04	4.45±0.30	0.51±0.04
F_7	3.28±0.04	4.60±0.24	0.48±0.05
F_8	3.34±0.05	5.02±0.18	0.42±0.01

Table 5 - Results of flow properties of spherical agglomerates

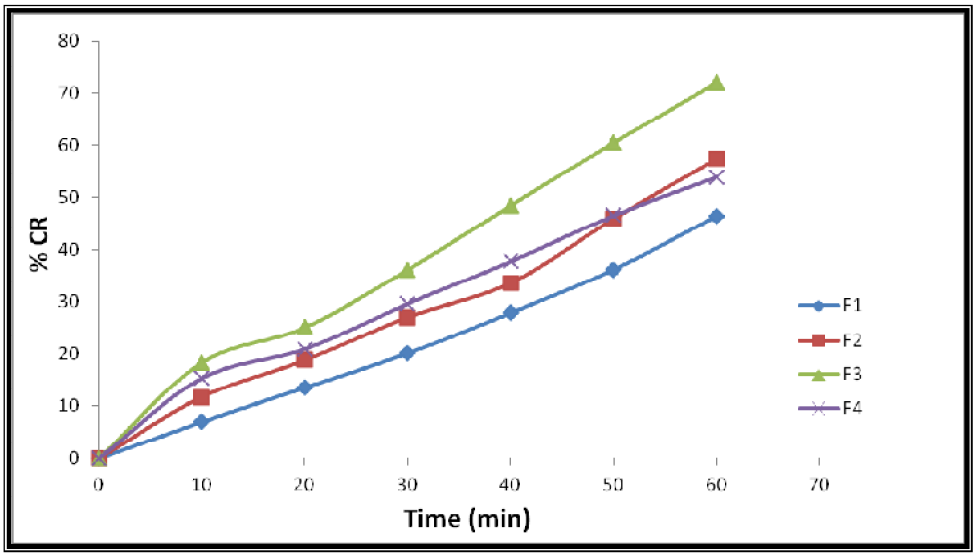
Formulations	Bulk density* $(gm/cc)^3$	Tapped density* $(gm/cc)^3$	Carr's index (%)	Hausner's ratio	Angle of repose
Pure drug	0.24±0.06	0.45±0.06	46.6	1.87	30°
F_1	0.27±0.05	0.32±0.08	15.6	1.18	16.5°
F_2	0.24±0.06	0.26±0.05	7.7	1.08	13.2°
F_3	0.33±0.05	0.35±0.04	5.7	1.06	14.1°
F_4	0.35±0.08	0.37±0.05	5.4	1.05	12.3°
F_5	0.27±0.07	0.29±0.03	6.4	1.07	15.6°
F_6	0.32±0.06	0.33±0.04	6.1	1.03	14.2°
F_7	0.36±0.02	0.38±0.08	5.2	1.05	12.6°
F_8	0.42±0.04	0.43±0.05	2.3	1.02	10.3°

Table 6: Results for weight variation and disintegration time

Formulations	Weight variation(%)	*In vitro* disintegration time(seconds)*
F_1	0.52	546
F_2	0.64	605
F_3	0.75	685
F_4	0.96	760
F_5	0.68	558
F_6	0.70	630
F_7	0.67	754
F_8	0.73	765

Table 7- Dissolution data for F1, F2, F3, and F4 in pH 1.2 HCl bufferTable

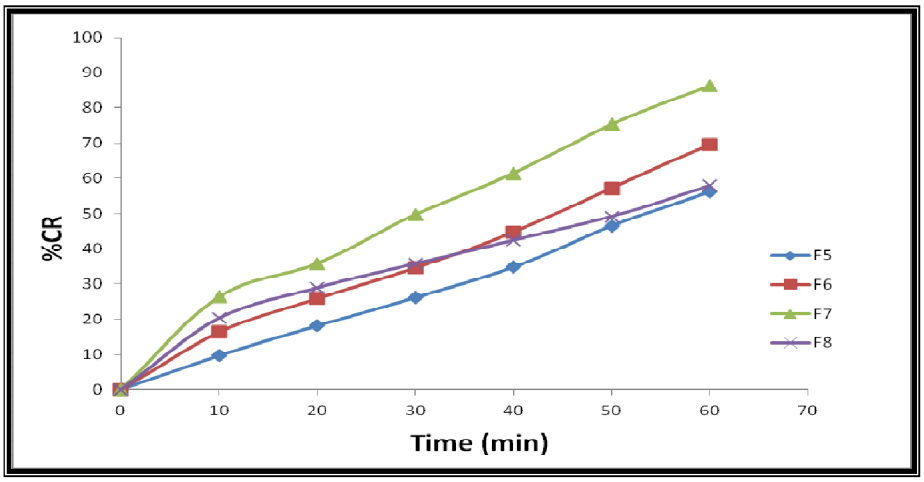
Time (min)	% Cumulative Release*			
	F1	F2	F3	F4
0	0	0	0	0
10	6.78	12.73	16.25	15.54
20	12.26	17.91	25.45	21.12
30	19.38	25.68	37.33	29.50
40	26.52	33.63	45.54	37.46
50	37.34	44.73	58.56	46.75
60	45.15	55.14	68.08	56.78



Graph 4: Dissolution profile of Telmisartan tablets containing agglomerates in batches F1, F2, F3 and F4

Table 8- Dissolution data of tablets containing agglomerates of batch F5, F6, F7 and F8.

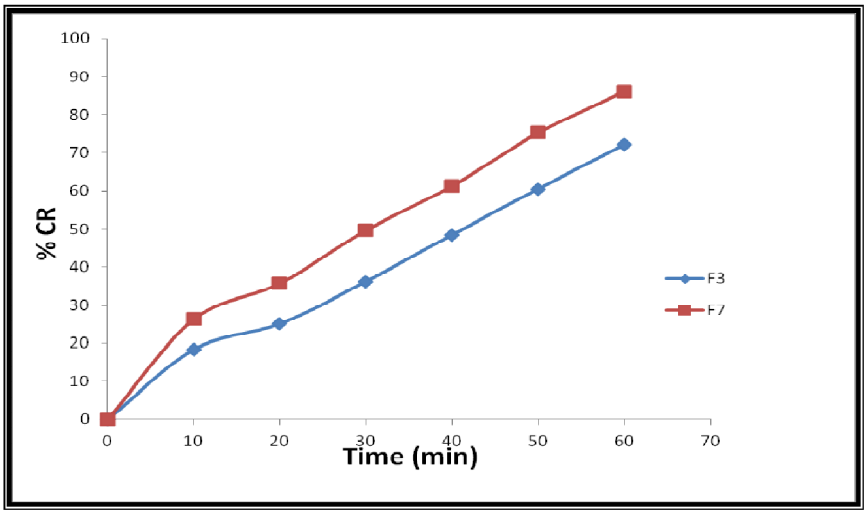
Time (min)	% Cumulative Release*			
	F5	F6	F7	F8
0	0	0	0	0
10	8.56	16.28	26.37	20.27
20	17.12	25.90	35.74	26.82
30	28.45	34.46	48.69	34.45
40	34.58	44.70	62.45	44.25
50	47.68	57.22	72.23	48.45
60	57.28	67.23	87.23	58.78



Graph 5: Dissolution profile of Telmisartan tablets containing agglomerates in batches F5, F6,F67 and F8

Table 9: Comparative dissolution data of tablets of batch F3 and F7

Time(min)	% Cumulative Release*	
	F3	F7
0	0	0
10	16.25	26.37
20	25.45	35.74
30	37.33	48.69
40	45.54	62.45
50	58.56	72.23
60	68.08	86.17

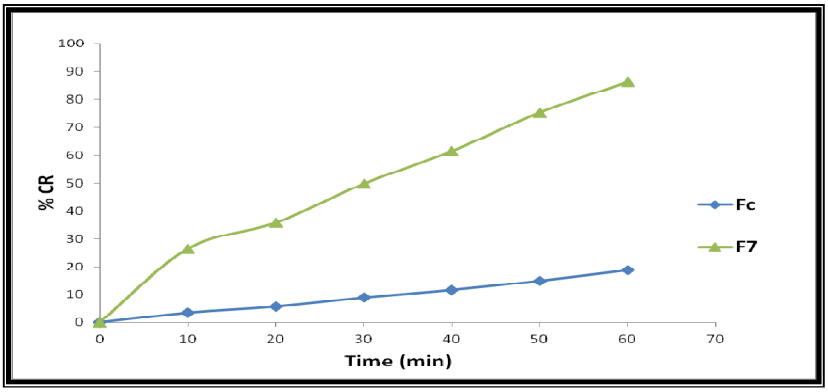


Graph 5 -Comparative dissolution profile of tablets of batch F3 and F7.

Table 10 - Comparative dissolution data of F7 with conventional telmisartan tablets

Time(min)	% Cumulative Release*	
	Fc	F7
0	0	0
10	4.45	26.37
20	6.71	35.74
30	8.48	48.69
40	12.39	62.45
50	15.53	72.23
60	19.78	86.17

***=Average of 3 readings**



Graph 6- Comparative dissolution profile of F7 with conventional telmisartan tablets

RESULTS: Standard curve:

The UV spectrum of Telmisartan indicates that the drug had a λ_{max} of 291 nm which was close to the reported values. The calibration curve in pH 1.2 HCl buffer was found to be linear over a concentration range of 2-10 µg/ml with r^2=0.9998.

Preformulation and solubility studies:

During preformulation studies of telmisartan revealed that drug had Hausner's ratio of 1.69 and Carr's index of 40.9% with a angle of repose of 32^0. These values indicate that the drug has very poor flow properties which can pose a problem in direct compression. Solubility studies indicated that the aqueous solubility of the drug in water was 8.34±0.06 µg/ml, where as solubility in pH 1.2 HCl buffer was 22.67±0.09µg/ml suggesting that the drug was insoluble in water but soluble in pH 1.2 HCl buffer.

FT-IR study:

The IR spectrum of telmisartan revealed the presence of peak at 3058.55 cm^{-1} which is due to C-H stretch present in aromatic group. The peak at 2959.23 cm^{-1} can be assigned to C-H stretch, while the peak displayed at 1696.09 cm^{-1}could be due to C=O stretching.

These characteristic peaks of the drug were also observed in spectrum of the formulation. So presence of these characteristic peaks of telmisartan in physical formulation reveals that the drug remains intact in formulation and there is no interaction between drug and polymer. The study also ruled out the incompatibility between the drug and other polymers used in formulating the spherical agglomerates.

Optimization parameters:

Different polymers were tried to prepared agglomerates of telmisartan, among them PEG-6000 and PVP K30 was found to be most suitable. Formulations F1 to F4 were prepared using PEG-6000 and F5 to F8 with PVP K30 in different concentrations.

In formulations F1 to F4 the flow properties of the agglomerates were found to be excellent as indicated by Carr's index (≤10 %), Hausner's ratio (1.0-1.11) and angle of repose (<20). Agglomerates were compressed into tablets and the tablets were evaluated for friability, hardness, disintegration time, thickness, weight variation and *in vitro* drug release. All the results obtained were conformed to the specifications mentioned in the IP.

In formulations F5 to F8 the flow properties of the agglomerates were also found to be excellent as indicated by Carr's index (≤10 %), Hausner's ratio (1.0-1.11) and angle of repose (<20). Agglomerates were compressed into tablets and the tablets were evaluated for friability, hardness, disintegration time, thickness, weight variation and *in vitro* drug release. All the results obtained were conformed to the specifications mentioned in the IP. The percentage cumulative release of Formulations F5, F6, F7 and F8 was found to be 57.28%, 67.23, 87.23% and 58.78% after 60 minutes respectively. (Formulation F7 was found to give highest cumulative release).

However compared to F1-F4 a moderate improvement in percentage cumulative release was observed. The percentage cumulative release increased with increasing concentrations of PVP-K30 except formulation F8.

Thus agglomerates containing polymers were found to be better flow properties compared to pure drug and also better drug release compared to conventional tablets of Telmisartan.

Among the two polymers used, formulations F7 prepared by using PVP K30 were found to be satisfactory in both flow properties and percentage. Hence, it was considered as the optimized formulation.

All the above results indicated that the formulated spherical agglomerates exhibited improved micromeritic and dissolution properties.

CONCLUSION

From the present studies, it can be concluded that the Spherical Agglomeration technique is a highly efficient technique to produce directly compressible spherical agglomerates of Telmisartan. The agglomerates drastically improved micromeritic properties of the drug and possessed higher solubility profiles which in turn, improved the dissolution rates of the drug. The prepared agglomerates were directly compressible owing to their altered flow properties and compaction behavior. Thus, the process of SA is likely to have a strong impact on formulation development and can be a useful tool to ensure greater precision for solid dosage forms of poorly compressible drugs.

References

1. Lachmann L, Libermann H. The theory and practice of industrial pharmacy. New Delhi: CBS Publications; 2009.293-297.
2. Yadav AV and Yadav VB. Designing of pharmaceuticals to improve physicochemical properties by spherical crystallization techniques. J of Pharm Res 2008;1:105-112. 3.
3. Chourasia MK, Jain NK, Jain S, Jain NK, Jain SK. Preparation and characterization of agglomerates of flurbiprofen by spherical crystallization technique. Indian J Pharm Sci 2003;65:287-91.
4. Paradkar AR, Pawar AP, Jadhav NR. A novel particle engineering technique. Asian J Pharm 2010; 4:4-10.
5. Mahanty S, Sruti J, NiranjanPatra Ch, Bhanoji Rao ME. Particle Design of drugs by Spherical Crystallization Techniques. Inte J Pharm Sciences and Nanotechnology 2010; 3:912-14.
6. Kallies B, Konig A, Ulrich J. Solidification by crystallization in dropsm international workshop for industrial crystallization, Breman, Germany. 1993:138.
7. Patil BP, Gupta VRM, Udupi RH, Srikanth K, Sree Giri Prasad B. Spherical Agglomeration- Direct Tabletting Technique. Inte Research J of Pharmacy 2011; 2:30-32.
8. Patil SV, Sahoo SK. Spherical crystallization: a method to improve tabletability. Research J of Pharmacy and Technology 2009; 2:234-37.
9. Aulton ME. Pharmaceutics-The Science of Dosage form Design. 2nd ed. NewYork: Churchill Livingstone; 2002.

10. Patel JK, Bodar MS, Amin AF, Patel MM. Formulation and optimization of mucoadhesive microsphere of Metaclopramide. *Ind J Pharm Sci* 2004;66(3);300-305.

11. Lachman L, Lieberman HA, Kanig JL. The Theory and Practice of Industrial Pharmacy. 2nd ed. Bombay: Varghese Publishing House; 1976: 69.

12. Khan KA, Sarfaraz MD, Doddayya H. Design and evaluation of Aceclofenac fast dissolving tablets prepared by crystallo-co-agglomeration technique. Int J Pharm Pharm Sci 2011;3: 116-123.

13. Chatwal GR, Anand SK. Instrumental methods of chemical analysis. 5th ed. New Delhi: Himalaya Publishing House; 2008: 2.42-2.45.

14. Lieberman HA, Lachman L. Pharmaceutical dosage forms: Tablets. 2nd ed. New York: Marcel Dekker; 1990: p.299-333.

15. Kausalya J, Suresh K, Padmapriya S, Rupenagunta A, Senthilnathan B. Solubility and dissolution enhancement profile of telmisartan using various technique. Inte J Pharm Tech Research 2011;3: 1737-49.

16. Martin A. Physical Pharmacy. 4th ed: Lippincott Williams and Wilkins; 2005: 46-48.