International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 6 Nov-Dec 2023, pp: 110-115 www.ijprajournal.com ISSN: 2249-7781

"Design and Characterization of Microcrystals of Amlodipine for Enhancement of Solubility"

Theerthesh KV *, Venkatesh, Nagendra R, Tanuja A J, Hanumanthachar Joshi
Department of Pharmaceutics, Sarada Vilas College of Pharmacy, Mysore, Karnataka, India

Submitted: 10-11-2023 Accepted: 20-11-2023

ABSTRACT
Poor aqueous solubility and bioavailability of drugs are one of the important factors affecting the absorption of drugs and consequently their therapeutic effectiveness. Reduction of particle size micro crystallization technique has new opportunities for poorly aqueous soluble drugs. The solubility problem can be solved by changing the crystal habit of drug. The anti solvent crystallization has been widely used for micro crystallization of the drugs in the presence of polymers for increasing the dissolution rate of poorly aqueous soluble drugs. Amlodipine is an anti-hypertensive drug. It is almost widely used calcium channel blocker the objectives of present work are to formulate and evaluate microcrystals of Amlodipine in order to enhance the solubility, which may result in enhanced absorption and there by improved bio availability. Amlodipine microcrystal were prepared by antisolvent crystallization method using Hydroxy propyl methyl cellulose (HPMC K4M), Poloxamer 407 and Polyvinyl Pyrolidine K30(PVP K30) as stabilizing agent the designed microcrystals were evaluated for various parameters like particle size, shape, surface morphology, drug content, FTIR, solubility studies, powder x ray diffractometry, disintegration test, in vitro drug release study and stability studies. The Amlodipine microcrystals were found to be Columnar (Prismatic) in shape. And drug content was found to be in the range of 87%-95% among all formulation F1,F3 and F5 showed better drug release that is 94.5%,95.06% and 87.14% respectively. F3 is considered as the best formulations the data obtained from the solubility analysis and powder X-ray diffraction studies showed the evidence for the enhanced solubility thus the study suggests that microcrystals of Amlodipine is effective for increasing bioavailability.

Key words: Microcrystals, Crystal Habit, Amlodipine, Solubility, Enhancement, Bioavailability.

I. INTRODUCTION

Hypertension is multifaceted, insidious disorder associated with cardiovascular cerebral and renal vascular abnormalities. A number of oral antihypertensive drugs have been developed in order to improve bioavailability. Calcium channel blockers are widely used in the treatment of Hypertension.

Despite of tremendous advancement of drug delivery system, oral route is the most preferred route of administration and hence tablets are the most preferred dosage forms. The formulation of poorly soluble drugs for oral delivery now presents one of the major challenges to formulation scientists in the industry. In the biological classification system, drugs with low aqueous solubility and high permeability are categorized as class-2 drugs. Often solubility is a rate limiting step for absorption of these drugs. Thus, improvement of aqueous solubility in such cases is valuable goal of effectively formulate them into bioavailable dosage form.[1]

Though a number of oral administrable anti-hypertensive drugs with varying dosage form have been developed in order to reduce several complications of hypertension, not all are able all are able to improve patient compliance due to difficulty in swallowing, chewing in geriatrics and psychiatrics along with institutional patients suffering from nausea, vomiting and motion advance in age, sex, race, family history of hypertension, obesity, atherosclerosis, high salt diet and alcohol. Elevated blood pressure has been related to the risk of major coronary events, such as myocardial infraction and coronary death. It also relates to the amount by which blood pressure is elevated. Patients with a history of previous cerebrovascular disease or myocardial infraction show a direct association between blood pressure levels and risk of recurrent events.[2]

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 6 Nov-Dec 2023, pp: 110-115 www.ijprajournal.com ISSN: 2249-7781

Ranges of systolic blood pressure and Diastolic blood pressure.

Category	Systolic BP (mmHg)	Diastolic BP (mmHg)
Optimal BP	<120	< 80
Normal BP	<130	< 85
High-normal BP	130-139	85-89
Hypertension		
Grade 1(mild)	140-159	90-99
Grade 2(moderate)	160-179	100-109
Grade 3(severe)	≥ 180	≥ 110

Individual with severe hypertension may Experian's dizziness, blurred vision or headache; however, moderate hypertension is generally asymptomatic and is often detected only during a routine examination. In addition to follow up blood pressure measurements, patients with documented hypertension (>140/90 mmHg) should also receive further evaluation to identify

- Known causes of raised blood pressure (e.g., renal disease)
- Contributory factors (e.g., obesity, high salt, and /or alcohol intake)
- Complications of hypertension (e.g., previous stroke or left ventricular hypertrophy)
- Cardiovascular risk factors (e.g., smoking or a family history of CVD)

Method of preparation of amlodipine microcrystals by anti solvent crystallization.[3,4,5]

The drug was dissolved in an organic solvent and thoroughly mixed (organic phase), Stabilizing agent was dissolved in an aqueous solvent and mixed rapidly (Aqueous Phase) Aqueous phase was added to organic phase drop by drop under continuous stirring (600-800RPM) and mixture is stirred for 30 minutes at room temperature. The microcrystals formed was then collected by decantation, washed with water and dried at room temperature in desiccators.

METHOD FOR PREPARATION OF MICROCRYSTALS OF AMLODIPINE

Microcrystals of Amlodipine were prepared by 'Anti solvent Crystallization technique'. Six formulation using different polymers are prepared in the ratio of 1:1, 1:2.

Preparation of the Amlodipine Microcrystals.

Sl.NO	Formulation	Drug: polymer ratio(w/w)	Polymer used	Solvent:Antisolvent ratio(ml;ml)
1	**F1**	**1:1**	**HPMC K4M**	**1:5**
2	**F2**	**1:2**	**HPMC K4M**	**1:5**
4	**F3**	**1:1**	**Poloxamer 407**	**1:5**
5	**F4**	**1:2**	**Poloxamer 407**	**1:5**
6	**F5**	**1:1**	**PVP K30**	**1:5**
7	**F6**	**1:2**	**PVP K30**	**1:5**

Evaluation[6-12]

Evaluation of the prepared micro crystals.Fourier transform infrared spectroscopy (FT-IR)

FT-IR studies were conducted using FT-IR spectrophotometer. The spectrum was recorded in the region of4000cm1 and 400cm-1.

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 6 Nov-Dec 2023, pp: 110-115 www.ijprajournal.com ISSN: 2249-7781

Particle size

All the prepared batches were analysed for particle size by optical microscope. First the eye piece micrometre was calibrated using a stage micrometre and then on a clean glass slide a small quantity of microcrystals were placed using a thin brush. Then they were covered carefully with a cover slip and observed under 45X magnification. One hundred particles from each batch were counted and average particle diameter was found out by the formula.

Were, n= total no. of particles in that size range.
d= Diameter of the particles.
N= total no. of particles

Solubility studies

It determined by dissolving drug substance in water 0.1N HCl, phosphate buffer pH7.4, methanol, ethanol, DMSO, the solubility study was conducted taking excess amount of the drug in 10ml of solution. Then the samples were kept in the water bath shaker and agitated for 24hrs at 37±0.5^{0}C. The samples were filtered and suitably diluted. The samples were analysed spectrophotometrically at λ max. The concentration of drug was determined using respective standard graph.

Drug content

Equivalent to 10mg of weighed microcrystals were crushed in a glass mortar then the powdered microcrystals were suspended in the liquid then diluted suitably under phosphate buffer pH 7.4 and analysed for drug content. The drug content was analysed by UV spectrophotometer at 350 nm using phosphate buffer pH 7.4 as blank.

Flow property studies.

The drug and the microcrystals were studied for various flow properties like bulk density, tapped density, Hausner ratio and Carr's index

Percentage yield

The prepared and dried microcrystals of all batches were accurately weighed. The measured weight of prepared microcrystals was divided by the total amount of all the excipients and drug used in the preparation of the microcrystals, which give the total percentage yield of microcrystals.

In-Vitro DRUG RELAEASE STUDY

Thein-vitro dissolution studies were carried out using USP type -1 Dissolution apparatus for up to 1 hr. Capsule containing Amlodipine microcrystals was placed in dissolution apparatus containing 900ml 7.4 pH phosphate buffer which was maintained at 37±0.5^0 C and at a stirring speed of 50 rpm. 5ml samples were withdrawn at predetermined time intervals and same volume of fresh medium was replaced into the basket. Sample was withdrawn at time intervals of 5, 10, 20, 30, 40, 50 and 60 min. The concentration of drug released was estimated by using UV spectrophotometer at λ max 350 nm. Comparison studies of in-vitro drug release formulation F1, F3, F5 and pure drug were carried out in in-vitro dissolution apparatus type 1 using above procedure.

II. RESULTS AND DISCUSSION

Drug content studies

The drug content was found to be good and uniform among the different batches of the prepared samples and ranging from 87.33% to 98.15%

Percentage yield of Amlodipine microcrystals.

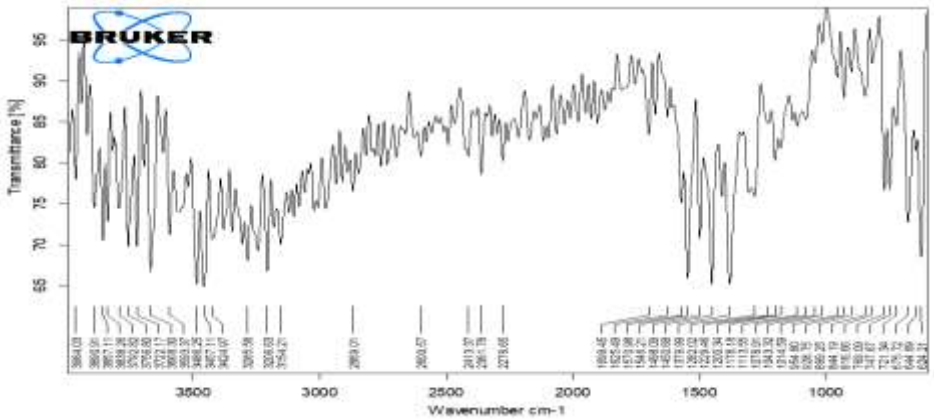
SL No.	Formulation code	% yield(w/w)	Drug content (mg)
1	F1	95.99	76.83±0.48
2	F2	98.15	73.70±0.74
3	F3	90.23	67.51 ±0.52
4	F4	89.33	66.21±0.35
5	F5	86.21	63. 35 ±0.23
6	F6	87.33	62. 53 ±0.18

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 6 Nov-Dec 2023, pp: 110-115 www.ijprajournal.com ISSN: 2249-7781

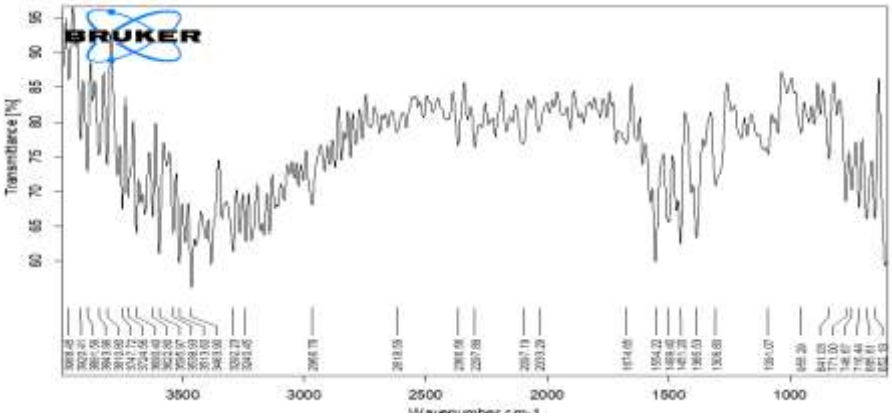
Fourier Transform Infrared Spectroscopy (FT-IR)

The IR spectra of the microcrystals also show the same characteristic bands. From the results obtained from IR spectra it can be concluded that there is no possibility of any interaction, chemical and functional group change during the processing of the formulation of microcrystals. Intensity of IR peaks of amlodipine microcrystals were decreased as compared to untreated drug, implying that the change in crystal habit and particle size reduction in microcrystals is responsible for these changes.

Description	Pure drug (cm^{-1})	Drug+HPMCK4M+Excipients (cm^{-1})	Drug+Poloxamer407+ Excipients (cm^{-1})	Drug+PVPK30+ Excipients (cm^{-1})
N-H	3292.21	3285.35	3245.00	3263.09
C-N	2127.70	2126.51	2126.71	2128.69
C=C	1676.98	1674.71	1673.76	1675.76
C-O	1091.11	1090.77	1078.22	1076.88
C-H	1385.28	1381.76	1379.56	1380.21
N-O	1550.34	1554.53	1549.66	1546.39



FTIR spectra of pure Amlodipine



FTIR spectra of Amlodipine and Poloxamer 407, Lactose and Mg.Sterate

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 6 Nov-Dec 2023, pp: 110-115 www.ijprajournal.com ISSN: 2249-7781

Flow property studies
Effect of various polymers on the bulk density, tap density, Hausner ratio and Carr's index..

Micromeritic properties of Amlodipine Microcrystals

Formulation code	Angle of Repose(θ^o)	Bulk Density(gm/ml)	Tapped density(gm/ml)	Carr's Index (%)	Hausner Ratio*
F1	25.07±0.24	0.44±0.02	0.56±0.031	17.3±0.4	1.12±0.01
F2	27.19±0.16	0.43±0.01	0.61±0.01	17.72±0.5	1.15±0.01
F3	27.09±0.45	0.43±0.01	0.51±0.02	15.02±0.4	1.17±0.03
F4	28.51±0.61	0.45±0.02	0.64±0.02	16.69±0.8	1.18±0.03
F5	29.12±0.26	0.60±0.02	0.48±0.02	15.43±0.3	1.18±0.07
F6	29.30±0.18	0.59±0.03	0.43±0.02	14.43±0.5	1.19±0.07

Solubility studies
The solubility studies were carried out using distilled water and 7.4 pH Phosphate buffersolubility profile of Amlodipine microcrystals prepared by Anti solvent Crystallization method**.**

Sl.no	Formulation code	Solubility(mg/ml)	
		Water	7.4 pH Phosphate buffer
1	**Pure drug**	**0.009**	**7.55**
2	**F1**	**0.776**	**13.45**
3	**F2**	**0.723**	**13.11**
4	**F3**	**0.620**	**11.92**
5	**F4**	**0.545**	**11.10**
6	**F5**	**0.432**	**8.92**
7	**F6**	**0.398**	**8.46**

IN-VITRO DISSOLUTION STUDIES

Time (min)	%cumulative Drug Realease			
	F1	F3	F5	Pure drug
0	0	0	0	0
5	41.37	42.16	22.49	15.17
10	48.24	48.81	38.63	20.32
20	54.61	60.02	53.72	27.31
30	64.34	68.07	62.70	32.56
40	72.36	76.23	68.48	40.23
50	82.57	84.04	76.63	45.53
60	94.55	95.06	87.14	49.28

Percentage cumulative drug realaease data of Amlodipine microcrystals from formulation F1,F3,F5 and pure drug.

III. CONCLUSIONS:

The microcrystals prepared using poloxamer 407 showed better dissolution rates when compared with that of other polymers.

REFERENCE

[1]. Haller H. Effective management of hypertension with dihydropyridine calcium channel blocker-based combination therapy in patients at high cardiovascular risk. International journal of clinical practice. 2008 May;62(5):781-90.

[2]. Sica DA. Pharmacotherapy review: calcium channel blockers. The Journal of Clinical Hypertension. 2006 Jan;8(1):53-6.
[3]. Reverchon E. Supercritical antisolvent precipitation of micro-and nano-particles. The journal of supercritical fluids, May 1, 1999; 15(1): 1-21.
[4]. Varin M, Migu SA, Barry D. Formation of Valine microcrystals through rapid antisolvent precipitation. J Dis Sci&Tech., 2008; 2(9): 617–20.
[5]. Seenivasan P, Haritha P, Chakal UMR. Design and Evaluation of aceclofenac microcrystals. J Pharm Res .March 2013;7:310-12.
[6]. Bhairav BA, Bachhav JK, Saudagar R. Review on solubility enhancement techniques .Asian J Pharm Res.2016;6(3):117-55.
[7]. Nagoba SN, Rao KP, Nagoba BS and Kasturi RM. Studies on Piroxicam Microcrystals for Improved Drug Therapy. Int J Res Pharm & Bio Sci. 2011;2(3):134-47
[8]. Sekhon BS. Pharmaceutical co-crystal a-review. Int J Pharm., 2009; 3(1): 2120-1.
[9]. Kapil K, Rai AK. Development and Evaluation of Microcrystals of Curcumin. Trop J Pharm Res. 2012 ;11 (5): 713-19.
[10]. Ala'a DN, Al-Khedairy EB. Formulation and evaluation of silymarin as microcrystals by in-situ micronization technique. Iraqi Journal of Pharmaceutical Sciences. 2019;28(1).
[11]. Nighute AB, Bhise SB. Preparation and evaluation of microcrystals of Cefuroxime axetil. Int J Pharm Tech Res 2009;1(1):424-30.
[12]. Dhanashree L, Bhujbal RK, RanpiseNS.Formulation and evaluation of Diacerein microcrystals using acetone and water as solvents' J Pharm Sci.2012; 48(1): 18-30.