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A RESEARCH ON IMPROVISATION IN DISSOLUTION OF OLMESARTAN MEDOXOMIL BY ENHANCING ITS SOLUBILITY USING SOLID DISPERSION TECHNIQUES

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ABSTRACT

Olmesartan Medoxomil a crystalline substance is a novel drug for the treatment of the hypertension. It is a BCS class II drug, having low aqueous solubility, exhibiting poor dissolution pattern. The purpose of the study was apply the solid dispersion(SD) techniques like kneading method and solvent evaporation method to enhance the solubility and dissolution rate of Olmesartan Medoxomil Solid dispersions were prepared by taking different ratio of drug and polymers by different solid dispersion techniques like kneading method and solvent evaporation method. The prepared solid dispersion were characterised for solubility study and *in-vitro* dissolution study. It was also characterized by Fourier transformation infrared spectroscopy (FTIR), differential scanning calorimetry (DSC) as well as X-ray powder diffractometry (XRPD). The XRPD spectra of solid dispersion indicated Olmesartan Medoxomil existed in amorphous state, this could be explained the fact that the aqueous solubility of Olmesartan Medoxomil was increased. It was found that saturation solubility, micromeritic properties and dissolution characteristics of solid dispersions were significantly improved than that of pure Olmesartan Medoxomil Hence it could be concluded that solid dispersions could be one of the effective approaches for improved performance of Olmesartan Medoxomil

Keywords:solid dispersion (SD), Novel Drug Delivery Systems (NDDS),Fourier transformation infrared spectroscopy (FTIR), differential scanning calorimetry (DSC) as well as X-ray powder diffractometry (XRPD).Olmesartan Medoxomil (OLM), Poloxamer- 188 (PXM- 188), Skimmed milk powder (SKM).

INTRODUCTION

Aqueous solubility and poor dissolution of insoluble drugs always remains a problem to the pharmaceutical industry. Lipophilic molecules especially those belonging to the biopharmaceutics classification system (BCS) class II and IV, dissolve slowly, poorly and irregularly, and hence poses serious drug delivery challenges like incomplete release from the dosage form, poor bioavailability, etc.

Oral formulation has been the preferred and most common route of drug delivery around the globe. The popularity of this dosage form is owing to its ease of administration and good patient compliance. From drug development and formulation perspective, a solid dosage form offers superior stability compared to intravenous formulations. Therefore, most of the new chemical entities (NCE) under development these days are intended to be used in a solid dosage form that originate an effective and reproducible in vivo plasma concentration after oral administration.[1]

Drug Solubility and Dissolution of Drug

Solubility is one of the key parameter in Biopharmaceutical Classification System (BCS), and dissolution rate is the most essential factor controlling the bioavailability of drugs. A compound with solubility of less than 1 part per 10,000 part of water is categorized as poorly water soluble drug.[1]

One of the important factors is solubility, especially aqueous solubility. A drug must possess some aqueous solubility for its therapeutic efficacy. For a drug to enter the systemic circulation to exert a therapeutic effect must be in solution form. In recent technologies, innovation of combinatorial chemistry and high through put screening can effectively discover the needs of new drugs, which present good pharmacological activities. However 35-40 % of these new drugs discovered by those technologies suffer from poor aqueous solubility.[2, 3]Modified Noyes-Whitney equation gives some hints as to how the dissolution rate of a very poorly soluble compound might be improved to maximize the oral bioavailability:

$$\frac{dc}{dt} = \frac{AD(CS-C)}{h} \quad (1)$$

Where,

dc/dt = rate of dissolution, A = surface area available for dissolution, D = diffusion co-efficient of the compound, Cs = solubility of compound in dissolution medium, C =

concentration of drug in medium at time't', h= thickness of diffusion boundary layer adjacent to the surface of the dissolving compound.

The method was termed as "solid dispersion". Solid dispersion is a promising drug delivery forms, which offer the possibility to disperse a hydrophobic drug in a hydrophilic matrix and thereby improve the dissolution rate and bioavailability of the drug. Olmesartan is a specific angiotensin II type I antagonist used alone or with other anti-hypertensive agents to treat hypertension. Olmesartan has poor aqueous solubility and low bioavailability of 26%. In the present study, an attempt was made to increase the solubility and dissolution rate of Olmesartan by solid dispersion technique using water soluble carrier's Skimmed milk powder and poloxamer-188, and crospovidone. The prepared solid dispersions were evaluated for drug content, *in vitro* dissolution rate studies, solubility studies, crystallinity studies and interactions between drug and carriers using IR, DSC and Powder X-ray diffraction study.

MATERIALS AND METHODS

Olmesartan Medoxomil was obtained as a gift sample from CTX life science Laboratories Ltd. Surat Gujarat India. Poloxamer-188, skimmed milk powder, Crospovidone, Lactose, magnesium stearate as well as colloidal silicon dioxide (aerosil)were provided from west-coast pharmaceutical LTD.All other chemicals were of analytical grade and all solvents were of HPLC grade.

Preparation of phosphate buffer (pH 6.8)

Phosphate buffer (pH 6.8) was prepared by the method described in Indian Pharmacopoeia. 50 ml of 0.2 M potassium dihydrogen phosphate was transferred to a 200 ml volumetric flask. After addition of 22.4 ml of 0.2 M sodium hydroxide, distilled water was added to make up volume and mixed thoroughly.

Construction of calibration curve in Phosphate Buffer pH 6.8

I. **Estimation of Olmesartan Medoxomil:** The standard calibration curve for Olmesartan Medoxomil was prepared in Phosphate buffer pH 6.8

II. **Standard Solution:** 100 mg of pure drug was dissolved in little quantity of methanol and transferred into in a 100ml volumetric flask and made up volume with phosphate buffer (pH 6.8) to give a concentration of 1 mg/ml.

III. **Stock Solution**: From the standard solution a stock solution was prepared to give a concentration of 100µg/ml in phosphate buffer (pH 6.8). Aliquots of 0.2, 0.4, 0.6, 0.8,

1.0, 1.2, 1.4, 1. de up to mark with solvent. The dilution gives 2µg/ml, 4µg/ml, 6µg/ml, 8µg/ml, 10µg/ml, 12µg/ml, 14µg/ml, 16µg/ml, 18 µg/ml of Olmesartan Medoxomil respectively.

The absorbance o6, 1.8 ml of stock solution were pipette out in 10 ml volumetric flasks. The volume was ma f prepared solution of Olmesartan Medoxomil in phosphate buffer (pH 6.8) was measured at 257 nm in UV\visible spectrophotometer against Phosphate buffer pH 6.8 as blank. The absorbance data for calibration curve yields a straight line, which shows that drug obeys Beer's law in the concentration range of 2-18 µg/ml.

METHODS OF PREPARATION OF SOLID DISPERSION

Olmesartan Medoxomil orodispersible tablet were prepared by different solid dispersion methods like Kneading, Solvent-evaporation methods.

Table 1: Composition of Olmesartan Medoxomil solid dispersions withSkimmed milk powder

Solid Dispersion	Method	Drug-polymer ratio	Formulation Code
Olmesartan Medoxomil : Skimmed milk powder	**Kneading method**	1:1	S1
		1:2	S2
		1:4	S3
		1:6	S4
		1:8	S5
	Solvent-evaporation method	1:1	E1
		1:2	E2
		1:4	E3
		1:6	E4
		1:8	E5

Kneading Method

The solid dispersion of drug with polymers like SMP and PXM-188 were prepared. Olmesartan Medoxomil : Polymers mixtures containing 1:1, 1:2, 1:4, 1:6 and 1:8 ratios in a mortar with methanol and water mixture (1:1, by volume). Then the wet mixture was kneaded thoroughly with a pestle to obtain a paste like consistency. The paste was then dried under

vacuum at room temperature, pulverized by passing through sieve no. 80 and stored in a dessicator till further use.[4]

Solvent Evaporation Method

Olmesartan Medoxomil and each of water soluble carriers SMP and PXM-188 were weighed accurately. Olmesartan Medoxomil : Polymers mixtures containing 1:1, 1:2, 1:4, 1:6 and 1:8 ratios transferred to china disc containing sufficient quantity of methanol to dissolve. The solvent was evaporated at room temperature. The resulting solid dispersion was stored for 24 h. in a desiccator to congeal. Finally, dispersion were passed through sieve no.80 and stored in desiccator till further use.[5]

Table 2: Composition of Olmesartan Medoxomil solid dispersions withPoloxamer-188

Solid Dispersion	Method	Drug-polymer ratio	Formulation Code
Olmesartan Medoxomil : PXM-188	**Kneading method**	1:1	K1
		1:2	K2
		1:4	K3
		1:6	K4
		1:8	**K5**
	Solvent-evaporation method	1:1	P1
		1:2	P2
		1:4	P3
		1:6	P4
		1:8	P5

CHARACTERIZATION OF PREPARED SOLID DISPERSION

Fourier Transform Infrared spectroscopy (FTIR)

The solid dispersion of Olmesartan Medoxomil were prepared in the form ofKBr pellets and subjected for scanning from 4000 cm^{-1} to 400 cm^{-1} using FTIR spectrophotometer. [6]

Differential scanning calorimetry (DSC)

Approximately 2 mg of Olmesartan Medoxomil or drug-carrier mixture was taken in aluminium pan, sealed with aluminium cap and kept under nitrogen purging (atmosphere). Both the samples were scanned from 50-400 °C with the scanning rate of 10 °C rise/min using differential scanning calorimeter. [6, 9]

Powder X-Ray Diffraction studies (XRD)

The powder XRD of the Olmesartan Medoxomil and solid dispersion formulations were recorded using an X-ray diffractometer. The scanning rate was 0.1º/sec and diffraction angle (2θ) was 0 to 50º. [6, 11]

Drug content

An accurately weighed quantity of drug-carrier mixtures equivalent to 20 mg of Olmesartan Medoxomil was taken in a 100 ml volumetric flask. The drug was then extracted by using methanol by subjecting to continuous shaking on a rotary shaker for 24 h. The concentration of Olmesartan Medoxomil in the extracted fluid was determined using UV-visible spectrophotometer (UV-1601, Shimadzu, Japan) against Phosphate Buffer pH 6.8 solutions as blank at 257 nm. [7, 10]

Saturation solubility studies

To evaluate the increase in the solubility of Olmesartan Medoxomil and its solid dispersion with SMP and PXM-188 solubility measurements were conducted. Excess amount drug or solid dispersion (equivalent to 20 mg drug) was added to 100 ml conical flask containing 25 ml distilled water. The system was agitated on a rotary shaker for 24 h at 100 rpm maintained at room temperature and filtered. The filtrate was suitably diluted and analyzed on a UV-Spectrophotometer at 257 nm. The studies were carried out in triplicate and the average value (± SD) was noted. [12, 13]

***In vitro* dissolution studies of Solid Dispersion of Olmesartan Medoxomil**

The quantity of solid dispersion equivalent to 20 mg of Olmesartan Medoxomil was placed in dissolution medium. The dissolution study of solid dispersion was conducted using dissolution testing apparatus II (paddle method) in 500 ml of phosphate buffer solution of pH 6.8 at 37±0.5 ºC and at a speed of 50 rpm. Aliquots of 5 ml was withdrawn at predetermined time interval and equivalent amount of fresh medium was replaced to maintain a constant volume after each sampling and analyzed spectrophotometrically at 257 nm against suitable blank using UV-visible spectrophotometer.[14, 15]

RESULT AND DISCUSSION

Organoleptic characteristics of Olmesartan Medoxomil

Table 3: organoleptic characteristics of drug

Drug	Test	Specification	observation
Olmesartan Medoxomil	Colour	White crystalline powder	White crystalline powder
	Taste	Characteristic	Characteristic
	Odour	Odourless	Odourless

In the organoleptic properties different test were performed such as colour, taste and odour. The result shows that Olmesartan Medoxomil is white crystalline powder with characteristic taste.

Physico-chemical characterization of Olmesartan Medoxomil

Table 4: physico-chemical characterization of the drug

Properties evaluated	Bulk density	Tapped density	Carr's Index	Hausner's ratio	Angle of repose
Result	0.56 Mg/ml	0.69 Mg/ml	20.35	1.29	38.50
Inference	---	---	Fair	Excellent	Passable

The results of physico-chemical characterization of Olmesartan Medoxomil shown in table.A flow property plays an important role in pharmaceuticals especially in tablet formulation because improper flow may cause more weight variation. It was found that its compressibility index is fair while its hausner's ratio was excellent and angle of repose were passable. This properties show that Olmesartan Medoxomil was good for direct compression.

CALIBRATION CURVE OF OLMESARTAN MEDOXOMIL

Table 5: Concentration and absorbance Obtained for calibration curve

Sl. No.	Concentration (µg/ml)	Absorbance (at 257 nm)
1	0	0
2	2	0.1023±0.003
3	4	0.1896±0.003
4	6	0.2863±0.002
5	8	0.3696±0.010
6	10	0.4566±0.013
7	12	0.5543±0.013
8	14	0.6456±0.016
9	16	0.7343±0.013
10	18	0.823±0.014

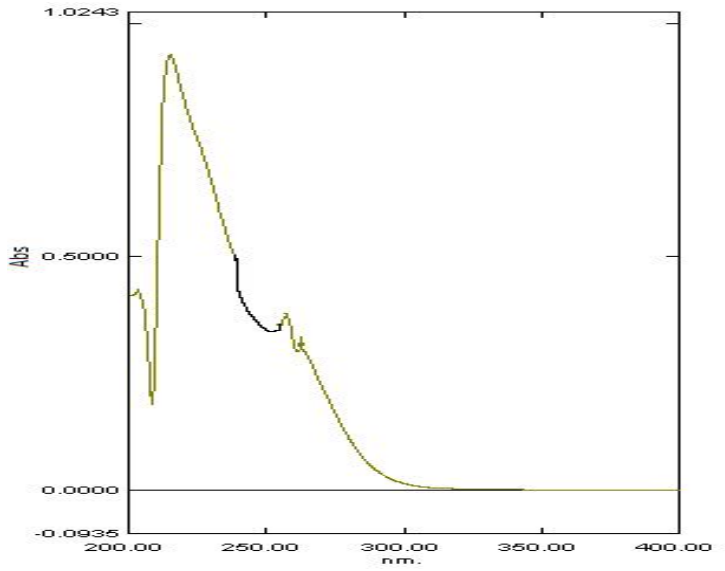
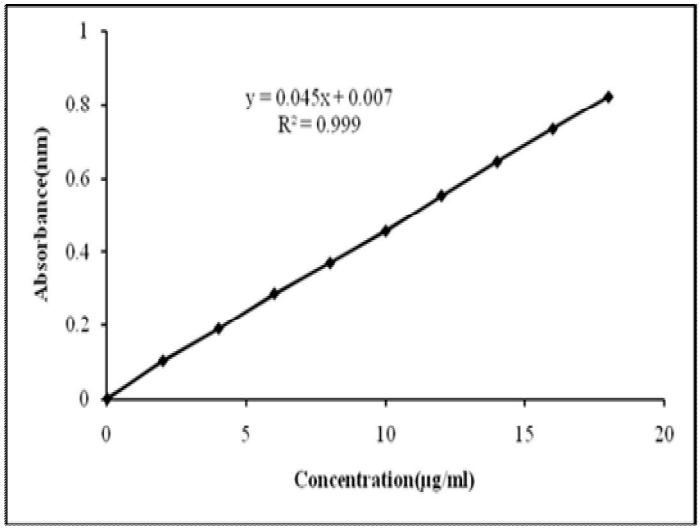


Figure 1: Absorption maxima of Olmesartan Medoxomil



Values are mean ± SD, n = 3.

Figure 2: Calibration curve of Olmesartan Medoxomil

The calibration curve of Olmesartan Medoxomil was developed in the range of 2 to 20 µg/ml at 257 nm. Good linearity with a regression coefficient of 0.999 (r^2 value) was observed. The tested concentration range obeyed Beer's law.

CHARACTERIZATION OF OLMESARTAN MEDOXOMIL AND ITS SOLID DISPERSION

INFRARED SPECTROSCOPY (IR) OF DRUG, AND PREPARED SOLID DISPERSION

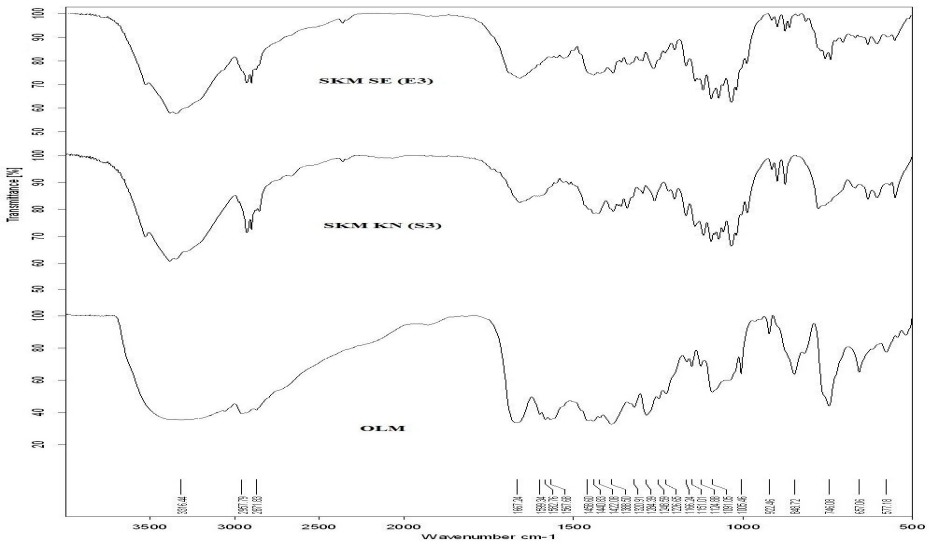


Figure 3: IR spectra of Olmesartan Medoxomil (OLM) and prepared solid dispersion by kneading method (SMP KN) andsolvent evaporation (SMP SE) method

Table 6: IR peak value of Olmesartan Medoxomil and prepared solid dispersions with skimmed milk powder

Functional groups (cm^{-1})	Olmesartan Medoxomil	SMP KN	SMP SE
C-H (aromatic)	*2957*	*2928*	*2929*
C-H (aliphatic)	*2871*	*2900*	*2900*
COOH (acid)	*1667*	*1658*	*1658*
C=C (aromatic)	*1599*	*1528*	*1568*
C=O	*1388*	*1383*	*1380*
C-N	*1483*	*1479*	*1475*

The following characteristic peaks were observed in IR spectra of Olmesartan Medoxomil and its Solid dispersion with SMP and poloxamer-188.

The characteristic absorption peak of OLM was obtained at 2957 cm^{-1}due to C-H stretching vibration of aromatic group. Other characteristic peaks were obtained at 2871 cm^{-1} due to C-H stretching of aliphatic group, -OH bending and –C=O stretching of –COOH acid at 1388cm^{-1}, C=C stretching of aromatic group at 1599 cm^{-1} and functional group of (-COOH) at 1667 cm^{-1} and 1483 cm-1 (C–N strech). IR showed all characteristics peaks of OLM. Hence, it conforms that the given sample was Olmesartan Medoxomil.

As seen in the above table, characteristics peak of pure drug Olmesartan Medoxomil and selected ratio of solid dispersion of olmesartan and skimmed milk powder prepared by different method were not deviate and it was nearly same of IR spectra of OLM. So there was no major sign of incompatibilities seen with skimmed milk powder thus as excipient can be used for the formulation.

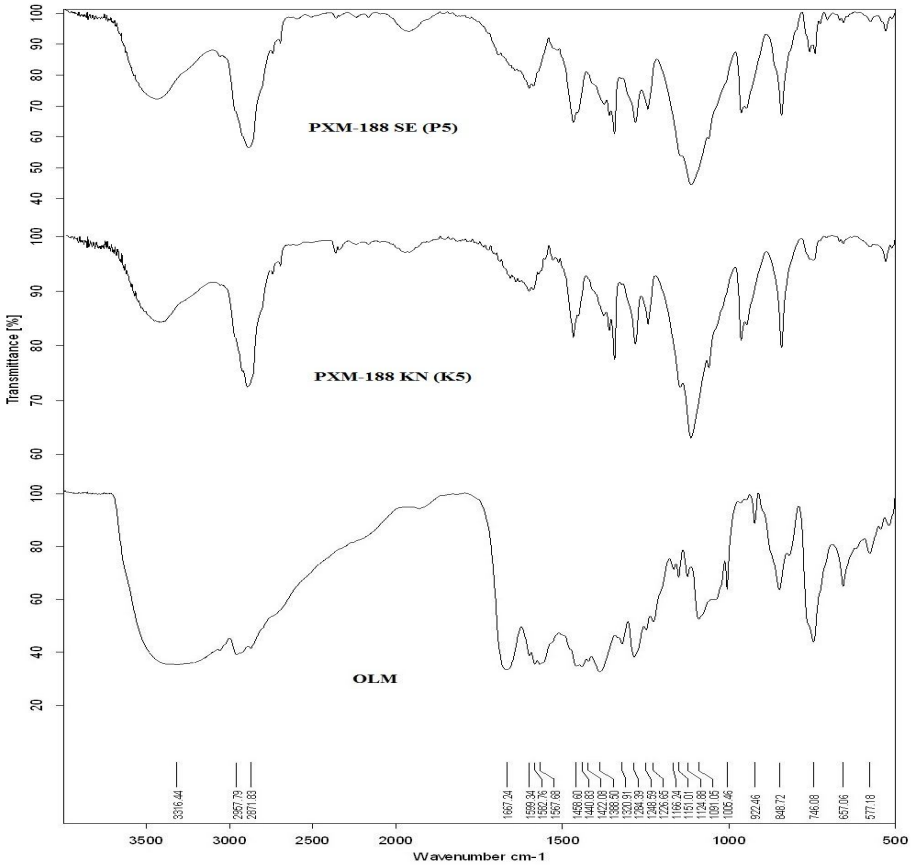


Figure 4: IR spectra of Olmesartan Medoxomil (OLM) and prepared solid dispersion by kneading method (PXM-188 KN) andsolvent evaporation method(PXM-188 SE)

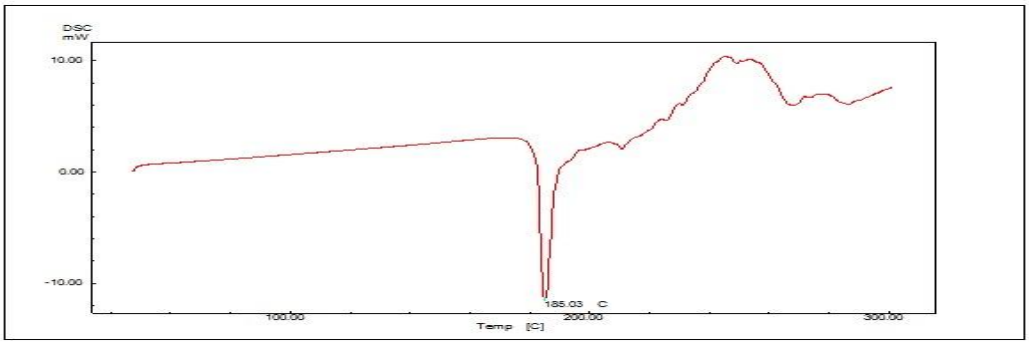
Table 7: IR peak value of Olmesartan Medoxomil and prepared solid dispersions with poloxamers-188

Functional groups (cm^{-1})	Olmesartan Medoxomil	PXM-188 KN	PXM-188 SE
C-H (aromatic)	2957	----	----
C-H (aliphatic)	2871	2829	2886
COOH (acid)	1667	1600	1600
C=C (aromatic)	1599	1467	1466
C=O	1388	1343	1343
C-N	1483	1470	1469

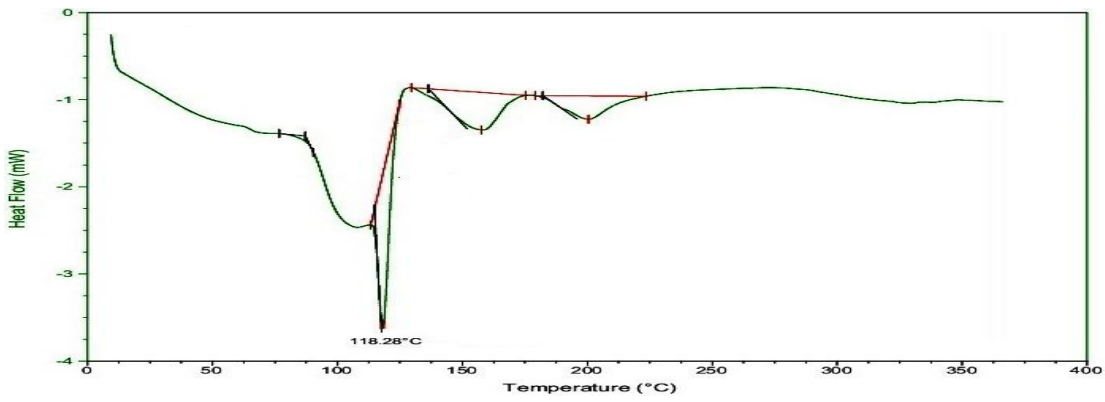
As seen in the above table, characteristics peak of pure drug Olmesartan Medoxomil and selected ratio of solid dispersion of olmesartan and skimmed milk powder prepared by different method were not deviate and it was nearly same of IR spectra of OLM. So there was no major sign of incompatibilities seen with skimmed milk powder thus as excipient can be used for the formulation.

DIFFERENTIAL SCANNING CALORIMETRY (DSC)

(A)



(B)



(C)

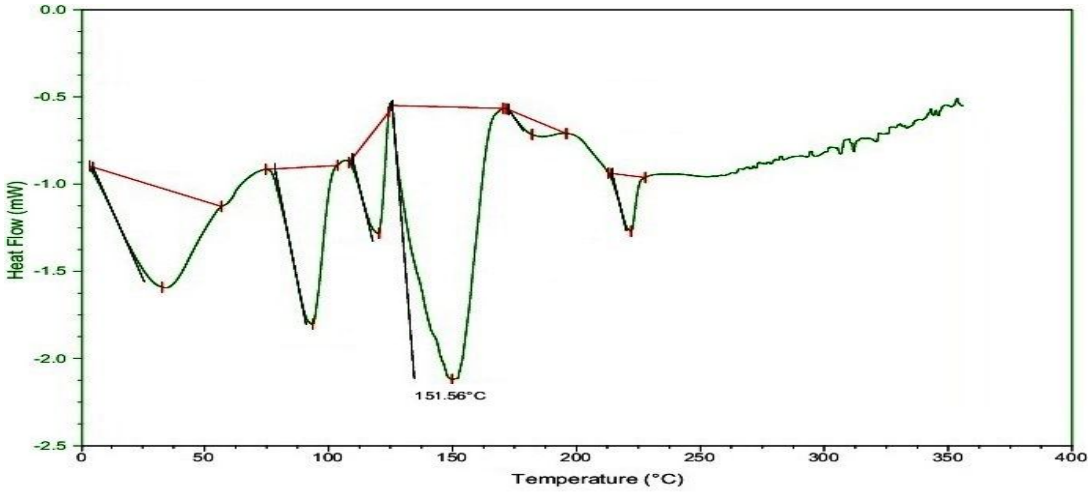
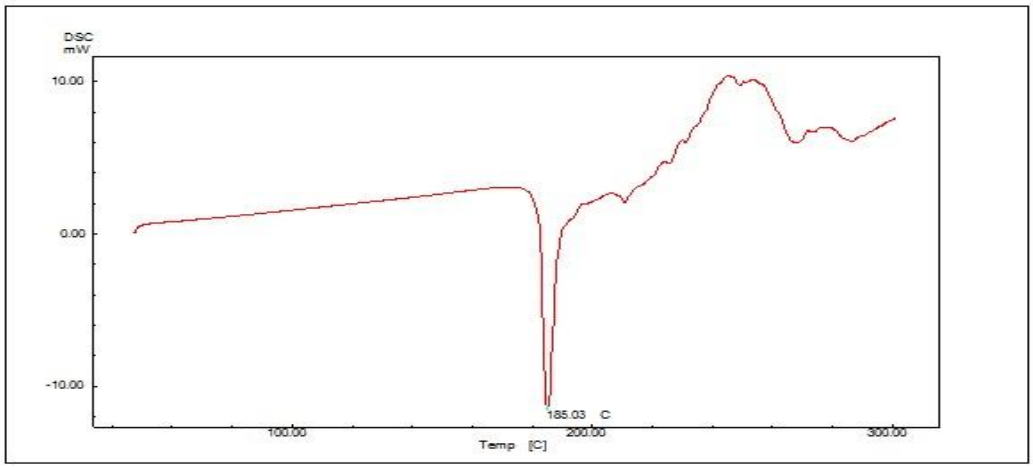
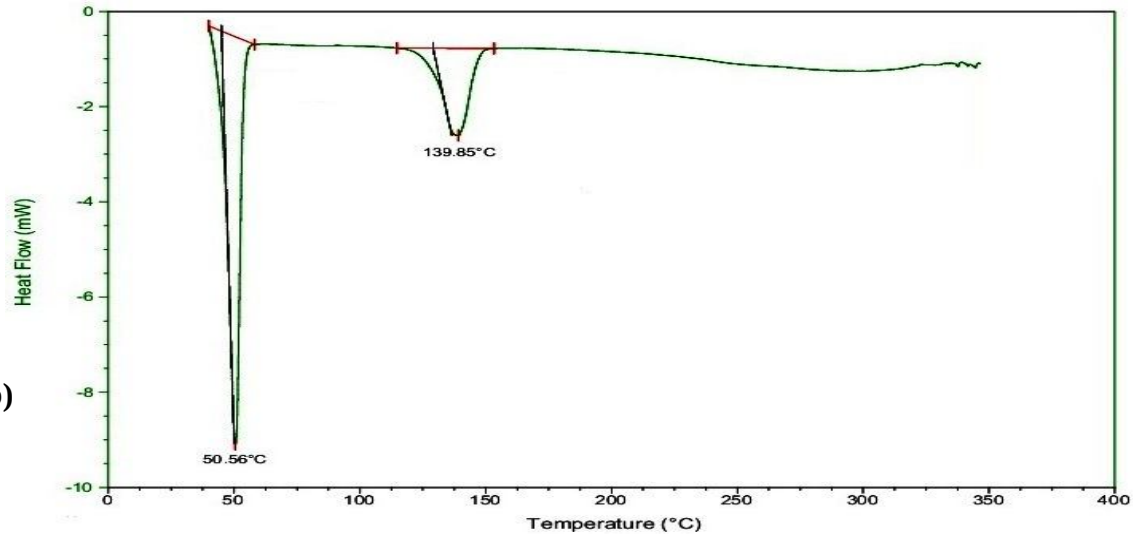


Figure 5: DSC thermogram of pure Olmesartan Medoxomil (A), prepared solid dispersion with Skimmed milk powder by Kneading method (B) solvent evaporation method(C)

(a)



(b)



(c)

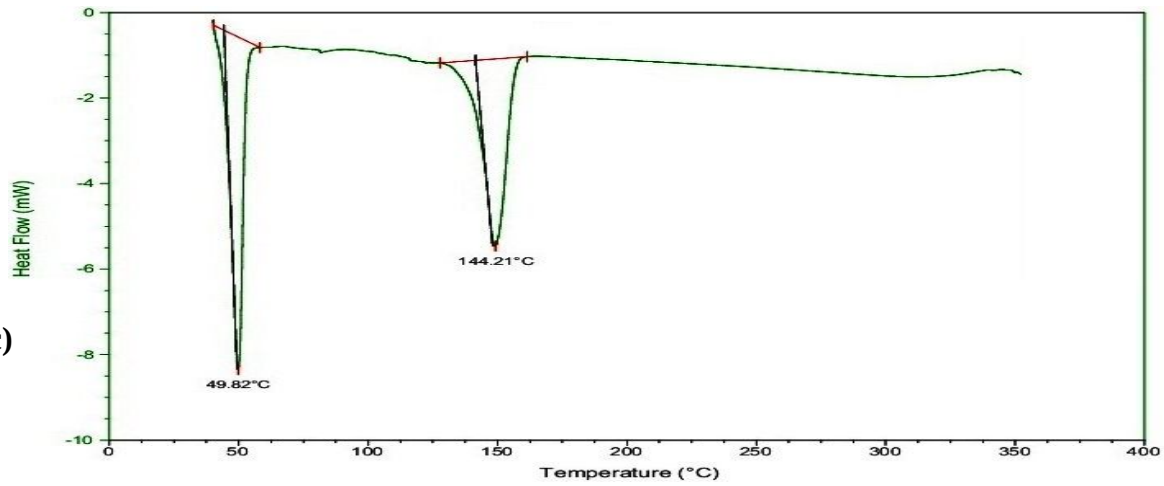


Figure 6: DSC thermogram of pure Olmesartan Medoxomil (a), prepared solid dispersion with poloxamer-188 by kneading method (b), solvent evaporation method (c)

Table 8: DSC peaks at different temperatures (^{O}C).

Contents	Endothermic peaks (^{O}C)
Pure drug	185.03
SMP KN	121.26
SMP SE	151.56
PXM KN	139.85, 50.56
PXM SE	144.21, 49.82

DSC was used to assess the thermal behavior of the drug (OLM) and its solid dispersion prepared. In figure, DSC thermogram of Olmesartan Medoxomil shows a single sharp characteristic endothermic peak corresponding to its melting, indicating its crystalline nature and a single peak indicates that the drug sample is free from impurities.

However, the characteristic endothermic peak corresponding to drug melting was broadened and shifted toward lower temperature with reduced intensity in the solid dispersion prepared by kneading and solvent evaporation method. This could be attributed to higher polymer concentration and uniform distribution of drug in the crust of carrier, resulting in complete miscibility of drug in the carrier.[49]

POWDER X-RAY DIFFRACTION PATTERN

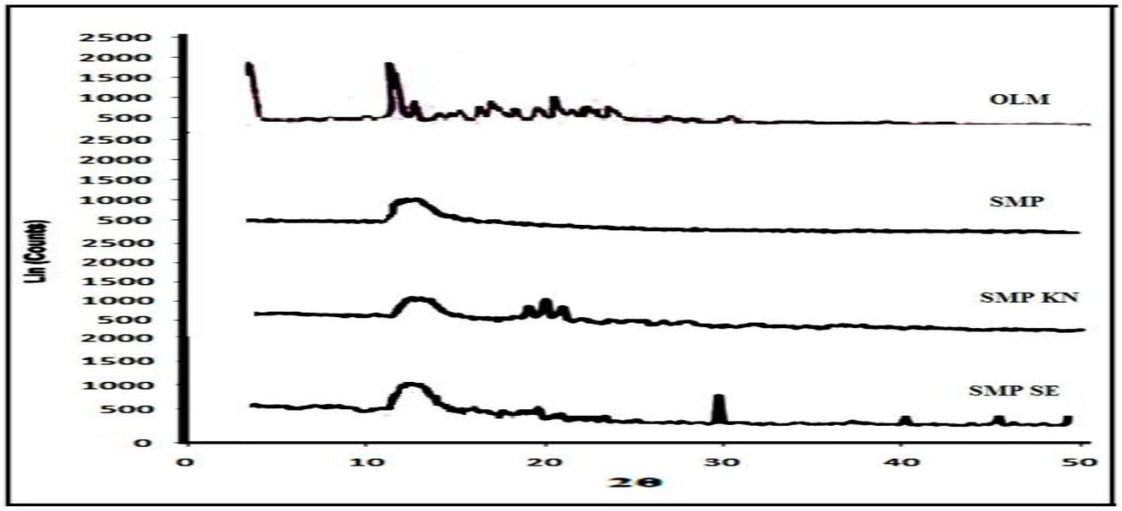


Figure 7: XRD pattern of Olmesartan Medoxomil, Skimmed milk powder, and solid dispersion by kneading method, solvent evaporation method

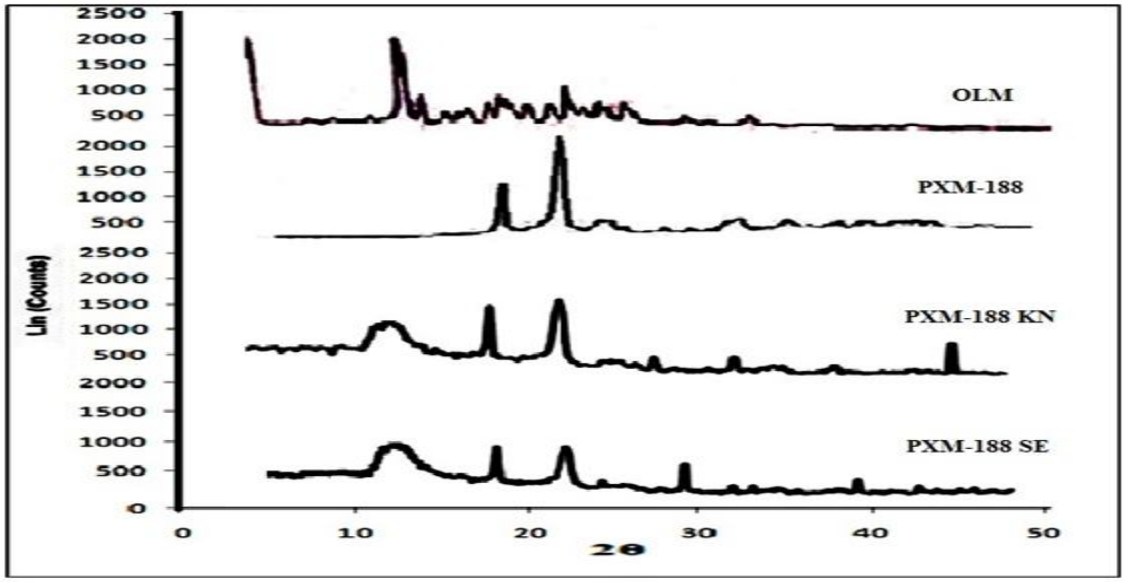


Figure 8: XRD pattern of Olmesartan Medoxomil, poloxamers-188, and solid dispersion by kneading method, solvent evaporation method

XRD patterns of Olmesartan Medoxomil, Skimmed milk powder, poloxamer-188 and its solid dispersion prepared by kneading and solvent evaporation methods is shown in Figure 21 and 22.The diffraction pattern of Olmesartan Medoxomil revealed several sharp high intensity peaks at diffraction angles (2θ) of 6.8, 9.7, 14.23, 14.2, 15.1, 16.2, 18.3, 20.7, 22.3, and 25.1 suggesting that the drug existed as crystalline material.

The XRD pattern of Olmesartan Medoxomil and its solid dispersion with Skimmed -milk powder and poloxamer-188 prepared by kneading and solvent evaporation methods.The few characteristic peaks of Olmesartan Medoxomil with considerable reduction in the peak intensity. This diminished peak suggests conversion of drug into amorphous form. This marked reduction in peak intensities provides an explanation for the significant increase in the dissolution rates by solid dispersion preparation.

Table 9: XRD peaks at different 2θ Values

Contents	2θ Values
Olmesartan Medoxomil	6.8, 9.7, 14.23, 15.1, 16.2, 18.3, 20.7, 22.3, 25.1
SMP	12.2, 12.6, 13.1, 13.3
PXM-188	18.9, 19.1, 22.3, 25.5
SMP KN	12.5, 14.4, 18.8, 20.4, 21.9
SMP SE	12.7, 13.3, 20.3, 22.6
PXM KN	13.9, 19.4, 24.9,25.3
PXM SE	13.6, 19.2, 24.6, 25.4

SOLUBILITY STUDIES

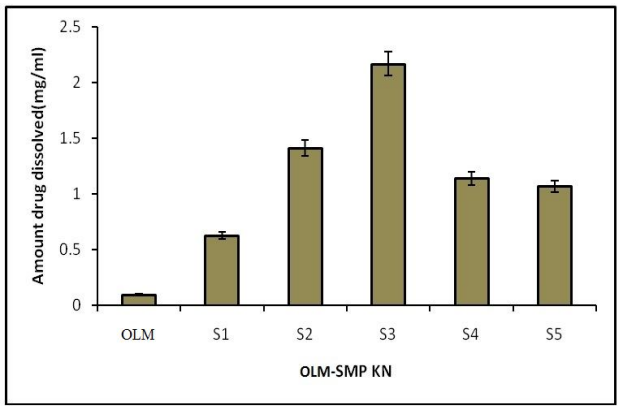
Table 10: Solubility studies of pure Olmesartan Medoxomil and its solid dispersion with skimmed milk powder and Poloxamer-188

Code	Solubility (mg/ml)
OLM	0.0096±0.0008
S1	0.62±0.015
S2	1.41±0.020
S3	2.17±0.017
S4	1.14±0.026
S5	1.07±0.020
E1	0.32±0.020
E2	0.85±0.015
E3	0.79±0.030
E4	0.32±0.010

E5	0.68±0.023
K1	0.60±0.010
K2	0.95±0.017
K3	1.26±0.010
K4	1.86±0.020
K5	2.24±0.017
P1	0.66±0.010
P2	0.88±0.017
P3	0.98±0.01
P4	0.63±0.032
P5	0.99±0.030

Values are mean ± SD, n=3

(a)



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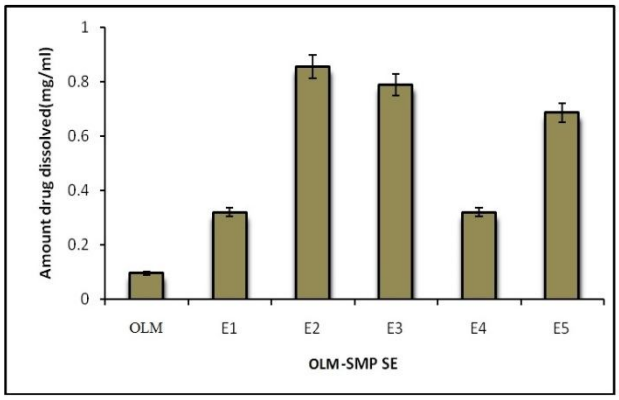
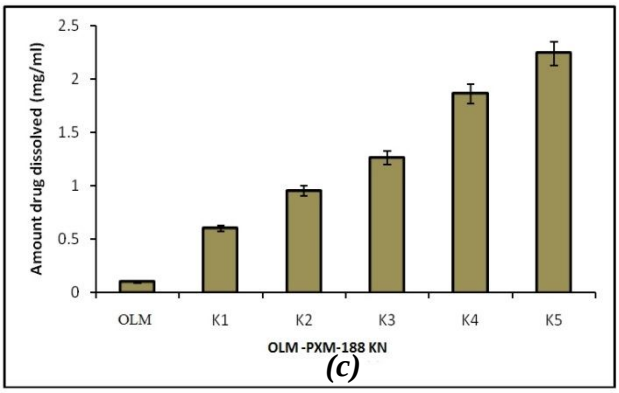


Figure 9: Solubility studies of Olmesartan Medoxomil and its solid dispersion with SMP by kneading method (a) and solvent evaporation method (b)



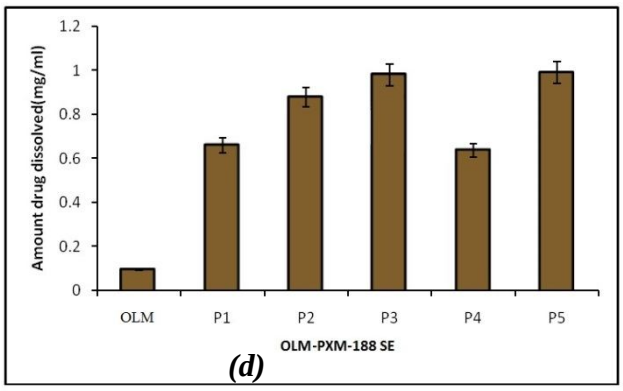


Figure 10: Solubility studies of Olmesartan Medoxomil and its solid dispersion with PXM-188 by kneading method (c) and solvent evaporation method (d)

The solubility of Olmesartan Medoxomil in distilled water was determined to be 0.0096 ± 0.0008mg/ml. While for kneading and solvent evaporation method with SMP and poloxamer-188 it was in the range of 0.62±0.015 to 1.07±0.020mg/ml, 0.32±0.020 to 0.68±0.023mg/ml, and 0.60±0.010 to 2.24±0.017 mg/ml, 0.66±0.010 to 0.99±0.030 mg/ml respectively.

All the drug-carrier mixtures showed an increase in drug solubility over crystalline OLM, Furthermore, enhancement in solubility of OLM was influenced by the concentration of polymers in the solid dispersion. With increase in polymers concentration, a predominant increment effect on solubility was observed.

IN VITRO DISSOLUTION STUDIES OF OLM AND ITS SOLID DISPERSIONS

Table 11: In vitro drug release profile of Olmesartan Medoxomil and its solid dispersion with Skimmed milk powder by kneading method

Time (min)	Cumulative % drug released					
	Drug	S1	S2	S3	S4	S5
0	0	0	0	0	0	0
5	10.61111	29.28071	33.9221	37.9941	29.19077	29.0023
10	12.21722	32.04894	39.5733	42.9932	35.8854	32.5746
15	13.78278	33.14449	42.5742	49.1254	40.7654	36.4231
20	15.25167	35.66235	47.8743	53.2285	44.921	40.7231
25	17.845	36.99979	50.4302	59.9909	47.8329	43.2947
30	20.90722	41.2938	54.39266	62.8854	49.6678	47.319
35	21.88722	47.3948	56.56544	67.8843	51.9587	50.0321
40	23.09722	51.2039	60.63795	71.347	54.329	52.4832
45	25.31722	56.3493	65.9822	76.58426	57.0032	57.3647
50	27.22389	60.4318	71.0098	88.84221	62.9332	63.9921
55	28.25833	63.2094	74.974	91.99458	70.997	67.8329
60	29.18944	65.3421	88.66879	92.4473	73.8976	69.3435

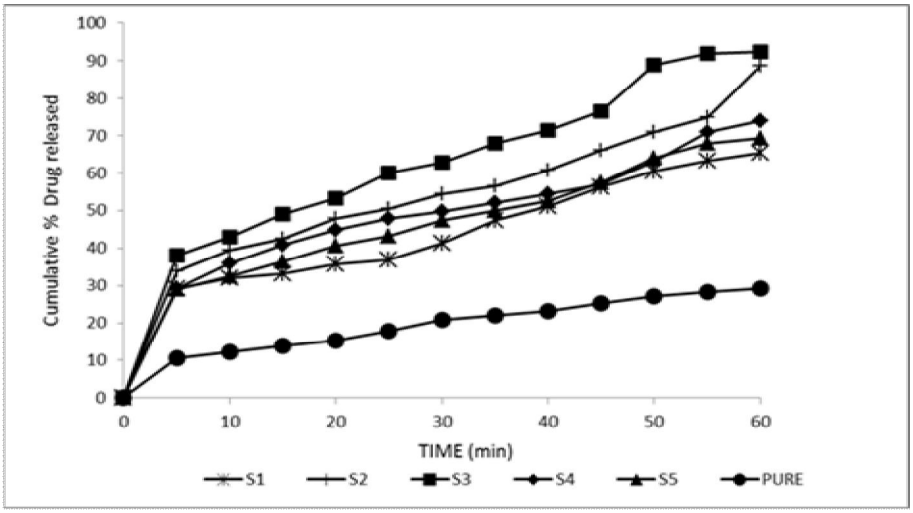


Figure 11: In vitro drug release profile of Olmesartan Medoxomil and its solid dispersion with Skimmed milk powder by kneading method

In vitro dissolution test results indicate complete dissolution of drug (OLM) from its solid dispersion within 60 minutes. It is observed that the drug and the formulation S1, S2, S3, S4 and S5 showed cumulative % drug release of 29.18944%, 65.3421%, 88.66879%, 92.4473%, 73.8976% and 69.3435% respectively.

Among from S1 to S5 batches the formulation S3 showed maximum release of 92.4473% in 60 min. Hence the S3 can be considered as good formulation because of its better release profile for the entire drug comprised within the solid dispersion of OLM and SMP by kneading method.

Table 12: *In vitro* drug release profile of Olmesartan Medoxomil and its solid dispersion with Skimmed milk powder by solvent evaporation method

Time (min)	Cumulative % drug released					
	Drug	E1	E2	E3	E4	E5
0	0	0	0	0	0	0
5	10.61111	29.28071	30.1584	31.4673	29.0023	29.19077
10	12.21722	32.04894	35.1659	33.5413	32.5746	35.8854
15	13.78278	33.14449	37.294	35.9234	36.4231	40.7654
20	15.25167	35.66235	40.0956	39.6548	40.7231	44.921
25	17.845	36.99979	49.5468	50.4302	43.2947	47.8329
30	20.90722	41.2938	54.5498	52.8876	47.319	49.6678
35	21.88722	47.3948	62.5498	56.56544	50.0321	51.9587

40	23.09722	51.2039	69.8649	60.63795	52.4832	54.329
45	25.31722	56.3493	75.1648	65.9822	57.3647	57.0032
50	27.22389	60.4318	83.1649	73.9987	63.9921	62.9332
55	28.25833	63.2094	86.2651	76.1287	67.8329	70.997
60	29.18944	64.3421	88.2654	78.3556	68.3435	71.8976

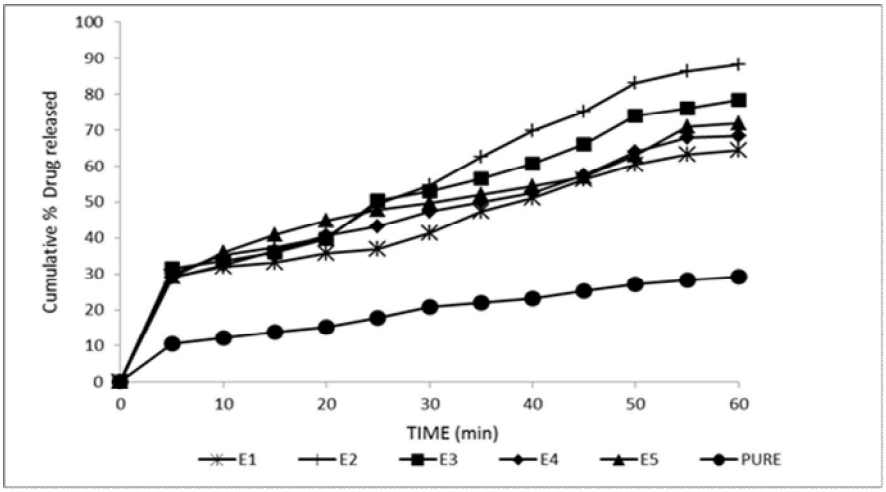


Figure 12: In vitro drug release profile of Olmesartan Medoxomil and its solid dispersion with Skimmed milk powder by solvent evaporation method

In vitro dissolution test results indicate complete dissolution of drug (OLM) from its solid dispersion within 60 minutes. It is observed that the drug and the formulation E1, E2, E3, E4 and E5 showed cumulative % drug release of 29.18944%, 64.3421%, 88.2654%, 78.3556%, 68.3435% and 71.8976% respectively.

Among from E1 to E5 batches the formulation E2 showed maximum release of 88.2654%, in 60 min. Hence the E2 can be considered as good formulation because of its better release profile for the entire drug comprised within the solid dispersion of OLM and SMP prepared by solvent evaporation method.

But amongst the two different methods with SMP and prepared by kneading and solvent evaporation methods. Kneading method was found to be most effective as it has shown maximum dissolution in phosphate buffer (pH 6.8).The formulation S3 showed rapid dissolution (60 min).

Table 13: In vitro drug release profile of Olmesartan Medoxomil and its solid dispersion with Poloxamer-188 by kneading method

Time (min)	Cumulative % drug released					
	Drug	**K1**	**K2**	**K3**	**K4**	**K5**
0	0	0	0	0	0	**0**
5	10.61111	29.28071	25.82904	29.19077	26.83616	**28.41171**
10	12.21722	32.04894	27.21033	32.20892	34.46092	**32.15364**
15	13.78278	33.14449	29.59374	33.25953	37.3923	**33.50968**
20	15.25167	35.66235	33.18734	35.97979	43.88065	**38.39154**
25	17.845	36.99979	36.68186	39.85438	50.4302	**43.95286**
30	20.90722	40.39819	38.49055	41.37044	54.39266	**52.10178**
35	21.88722	43.04901	40.31378	43.03079	56.56544	**57.4464**
40	23.09722	43.60068	41.49095	45.56819	60.63795	**63.30048**
45	25.31722	44.86102	44.06328	49.78921	72.98493	**76.58426**
50	27.22389	45.63477	47.9786	55.37802	76.03343	**88.84221**
55	28.25833	46.5535	49.2205	59.48866	78.51695	**91.99458**
60	29.18944	47.12356	50.27216	60.97546	88.66879	**95.74631**

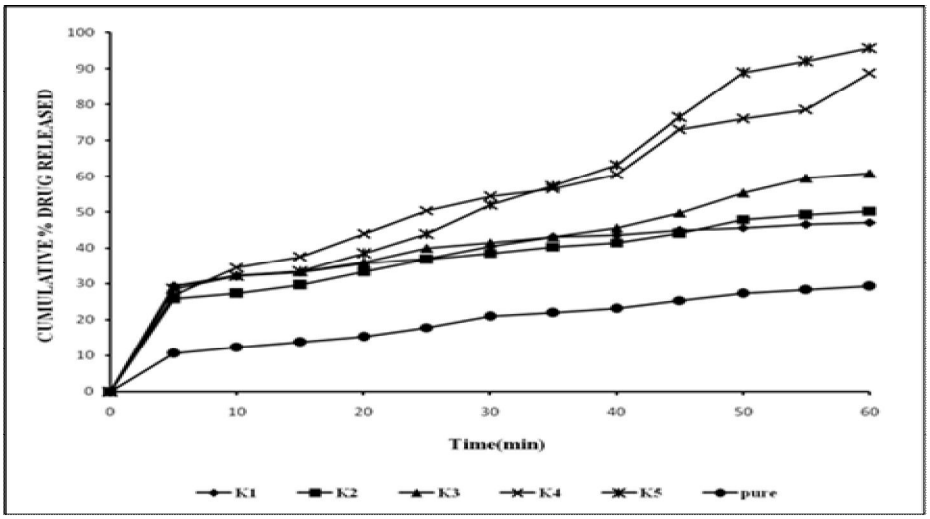


Figure 13: In vitro drug release profile of Olmesartan Medoxomil and its solid dispersion with Poloxamer-188 by kneading method

In vitro dissolution test results indicate complete dissolution of drug (OLM) from its solid dispersion within 60 minutes. It is observed that the drug and the formulation K1, K2, K3, K4 and K5 showed cumulative % drug release of 29.18944%, 47.12356%, 50.27216%, 60.97546%, 88.66879% and 95.74631% respectively.

Among the K1 to K5 batches the formulation K5 showed maximum release of 95.74631% in 60 min. Hence the K5 can be considered as good formulation because of its better release the entire drug comprised within the solid dispersion of OLM and PXM-188 prepared by kneading method.

Table 14: *In vitro* drug release profile of Olmesartan Medoxomil and its solid dispersion with Poloxamer-188 by solvent evaporation method

Time (min)	Cumulative % drug released					
	Drug	P1	P2	P3	P4	P5
0	0	0	0	0	0	0
5	10.61111	16.7264	37.28246	36.10953	61.27908	61.84688
10	12.21722	18.83513	38.6593	40.01202	65.93567	70.99595
15	13.78278	20.44056	39.77845	44.39259	67.83315	72.23289
20	15.25167	22.73223	41.37349	47.92765	71.60943	76.67413
25	17.845	27.50896	42.77979	51.99962	72.92833	78.48688
30	20.90722	31.06183	46.87349	56.55031	75.4977	80.84346
35	21.88722	35.69295	50.93708	59.56049	78.70785	83.7492
40	23.09722	39.39665	56.10776	62.2159	80.07652	85.07678
45	25.31722	45.52345	61.79384	65.84076	82.07353	86.94284
50	27.22389	50.13964	67.39759	74.68159	83.46087	88.81958
55	28.25833	55.02165	70.24029	78.5455	85.47655	91.7733
60	29.18944	56.96087	73.57363	83.07342	88.12679	93.14886

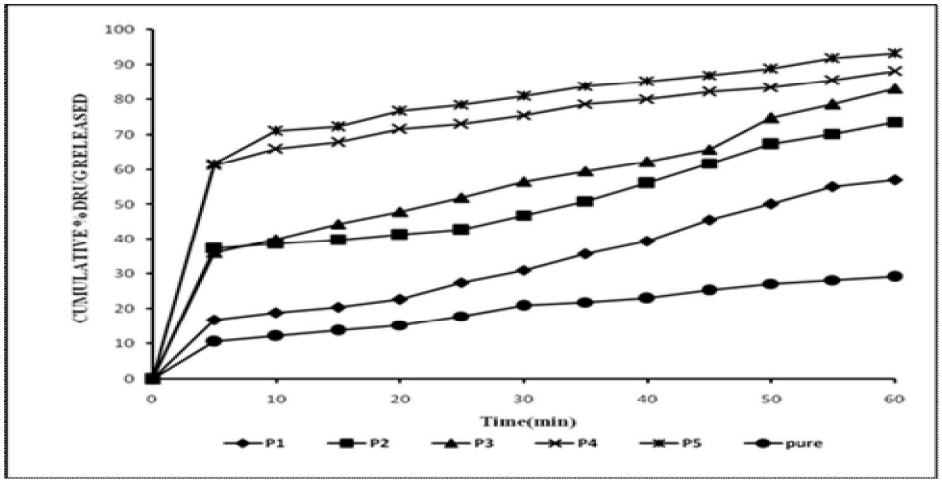


Figure 14: In vitro drug release profile of Olmesartan Medoxomil and its solid dispersion with Poloxamer-188 by solvent evaporation method

In vitro dissolution test results indicate complete dissolution of drug (OLM) from its solid dispersion within 60 minutes. It is observed that the drug and the formulation P1, P2, P3, P4 and P5 showed cumulative % drug release of 29.18944%, 56.96087%, 73.57363%, 83.07342%, 88.12679% and 93.14886% respectively.

Among from P1 to P5 batches the formulation P5 showed maximum release of 93.14886% in 60 min. Hence the P5 can be considered as ideal formulation because of its better release the entire drug comprised within the solid dispersion of OLM and PXM-188 prepared by solvent evaporation method.

But amongst the two different methods with PXM-188 and prepared by kneading and solvent evaporation methods. Kneading method was found to be most effective as it has shown maximum dissolution in phosphate buffer (pH 6.8).The formulation K5 showed rapid dissolution (60 min).

DISCUSSION

The solubility and dissolution rate of Olmesartan Medoxomil was significantly increased solid dispersion prepared by kneading method and solvent evaporation method compared to conventional method. The improvement of solubility and dissolution rate was found with Skimmed milk powder in ratio of 1:4 and with poloxamer- 188 in ratio of 1:8 in kneading method (92.4473%) and (95.74631) compare to conventional method (29.18944%) within 60 minute. FTIR and DSC study revealed no drug-polymer interactions. XPRD studies of solid dispersions conformed that conversion of crystalline drug into the amorphous form.

CONCLUSION

Solid dispersion of the Olmesartan Medoxomil with poloxamer-188 was prepared successfully by using kneading method. The resultant SD has the desired micromeritics and physicochemical properties such as solubility and dissolution. It is clear from the study of optimized batch that is solid dispersion withpoloxamer-188 exhibits faster release as compared to skimmed milk powder. Kneading method proved to be excellent technique for enhancement of solubility and dissolution of Olmesartan Medoxomil to solvent evaporation method.

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