Solubility Enhancement of Chlorzoxazone by Solid Dispersion Method and Fabrication of Immediate Release Tablet

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Abstract

The aim of present research work was to formulate and evaluate an immediate release tablet of Chlorzoxazone SD by direct compression, it is an API used in the treatment of muscle spasm. Chlorzoxazone is a BCS II drug with poor solubility and high permeability. Design-Expert® version13 software was used for designing 3^2 full factorial designs for selection of concentrations of Superdisintegrants i.e. SSG and CCS. Then formulated F9 batches were evaluated for Tablet Appearance, Weight Variation, Thickness, Hardness, Friability, Drug Content, Disintegration Test, Water Absorption Ratio, Uniformity of dispersion, *In-vitro* Dissolution Test and Stability Studies. Instrumental analysis viz. FTIR, DSC and XRD studies were carried out. F2 batch is an optimized batch, has shown most satisfactory results. Therefore, as per the findings, formulation met goals of increasing solubility, dissolution rate, % friability, hardness, water absorption ratio, convenience of administration, and safety.

Keywords: Immediate release, solid dispersion, solubility enhancement, kneading, Chlorzoxazone

Introduction

Immediate release tablet is one of the most practical and effective ways to administer drug is orally (1). When patients needed more traditional ways to take their drug during an emergency, the idea of immediate release tablets was developed (2). Recent years have seen an increase in the adoption of novel drug delivery methods, such as immediate release tablets (3). Disintegration is a vital step in the rapid release tablet because it increases drug dissolution and, consequently, bioavailability (4). There are only a few widely available super-disintegrant, such as crosscarmellose sodium, crospovidone, and sodium starch glycolate (5). Immediate release tablets have recently begun to acquire acceptance and popularity as a drug delivery system, primarily because they are simple to use, have a rapid onset of action, are affordable, and improve patient compliance (6). It is a novel technique for extending product life cycles, creating opportunities and expanding markets (7).

This research also aims to investigate the effects of formulation approaches on the release characteristics of immediate release tablets (8). The research seeks to shed light on the best formulation method for obtaining desired drug release characteristics through analysis (9). This study will discuss the importance of excipients choice in immediate release tablets in addition to formulation

(10). Excipients are essential for maintaining tablet integrity, enabling dissolution, and improving drugs dissolution (11). By investigating formulation design, formulation processes, excipients choice, and evaluation methods, this research seeks to advance our understanding of immediate release tablets (12). The results of this study may help pharmaceutical researchers and scientists create improved immediate release tablets that will improve patient outcomes and boost the overall efficacy (13). Different muscle in the body might experience muscle spasms in a variety of ways (14).

Materials and Methods

Chlorzoxazone was obtained as a gift sample from. All the excipients and solvents used are analytical grade

Methods of Preparation

Preparation of Solid Dispersion by Kneading Method

Solid Dispersion was prepared in the ratio of drug: carrier (1:1, 1:2, 1:3, 1:4) with PEG 4000. The weighed amount of drug and carrier i.e. Chlorzoxazone and PEG4000 were placed in a mortar and triturated with pestle for few minutes. Then definite amount of alcohol: water (1:1) was added and then triturated till it evaporate. Then the complex mixture was dried and passed through the 100# sieve and stored in dry area with no moisture for further use (15).

Table 1: Chlorzoxazone and Drug Complex.

Method	Drug to Carrier	Drug to Carrier ratio	Formulation Code
Kneading Method	CHLZ:PEG	1:1	SD1
	CHLZ:PEG	1:2	SD2
	CHLZ:PEG	1:3	SD3
	CHLZ:PEG	1:4	SD4

Table 2: Formulation table of Chlorzoxazone: PEG4000 Solid dispersion Immediate release tablet

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Complex Drug	500	500	500	500	500	500	500	500	500
Sodium Starch Glycolate	2	8	8	5	5	8	2	2	5
Croscarmellose sodium	2	5	3.5	3.5	5	2	5	3.5	2
Lactose	92	83	84.5	87.5	86	86	89	90.5	89
Talc	1	1	1	1	1	1	1	1	1
Magnesium stearate	3	3	3	3	3	3	3	3	3
Total Weight	600	600	600	600	600	600	600	600	600

**All values are expressed in mg/tablet*

Evaluation of Solid Dispersion

All prepared solid dispersion was evaluated for parameter as per IP.

Evaluation of Immediate Release Tablet

Pre- Compression Parameters (16-20)

Angle of repose (θ)

Funnel fixed method was used to determine angle of repose. The height of the glass funnel was adjusted such that tip of funnel reached apex of powder heap. Then powder was passed through funnel freely onto surface. The powder cone diameter was measured and angle of repose was calculated by equation.

$\theta = \tan^{-1} (h/r)$

θ is angle of repose, h is height unit is cms, r is radius unit is in cms

Bulk density

The ratio between mass of powder and bulk volume is bulk density. Denoted by unit gm/cc.

Tapped density

The ratio between the mass of powder and volume of powder after tapping is known as tapped density.

Expressed in terms of gm/cc.

$$Tapped\ density = Weight\ of\ powder / Tapped\ volume\ of\ powder$$

Carr's Index

Carr's Index is measured for property of powder to be compressed; they are measure of relative importance of inter particular interaction. It is calculated by using equation

$$Carr's\ Index = Tapped - Bulk\ density / Tapped\ density \times 100$$

Hausner's ratio

It is determined by measuring bulk density and tapped density of powder.

$$Hausner's ratio = Tapped\ density \div Bulk\ density$$

Result and Discussion

Organoleptic Properties (21)

Chlorzoxazone was evaluated for the organoleptic properties viz. Colour, odor, taste, melting point and saturation solubility studies, the results are as shown in Table 3

Table 3: Organoleptic Properties of API

Sr.no	Test	Observation
1.	Colour	White to off white powder
2.	Odor	Odorless
3.	Appearance	Crystalline Solid powder
4.	Taste	Bitter
5.	Melting Point	192^0C
6.	Saturation Solubility	Water - 0.031±0.1 mg/ml
		0.1N HCl- 0.041± 0.2 mg/ml
		pH 6.8 buffer- 0.037±0.1 mg/ml

Drug- excipients Compatibility studies by FTIR Spectroscopy- FTIR Studies (22)

FTIR studies of drug, polymer and physical mixture were carried out to check compatibility of an API with the carrier. It was concluded that the drug is compatible with carrier as no any profound changes were observed in the peaks of an API.

FTIR Spectrum of Chlorzoxazone is as shown in Fig. 1. The FTIR Spectrum data of Chlorzoxazone is as shown in Table 4 as follows:-

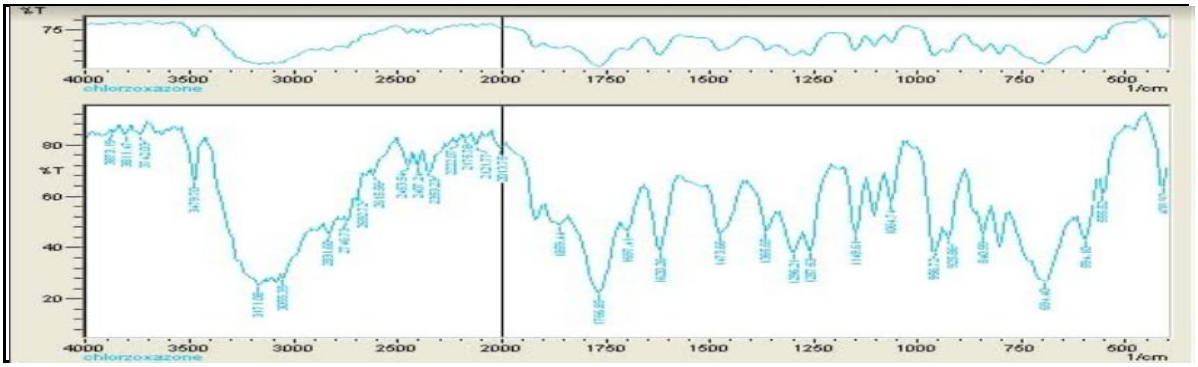

Fig. 1: FTIR Spectrum of Chlorzoxazone.

Table 4: FTIR Spectrum data of Chlorzoxazone.

Sr. No.	Functional Group Assigned	Standard Range of wave number (cm^{-1})	Observed Peaks at wave number (cm^{-1})
1	-NH group	3450-3350	3171, 3055
2	-CH, Ar	3000-3100	2831
3	C = O group	1650-1800	1766
4	C = C, Ar	1450-1600	1697
5	C – O – C group	1000-1300	1054

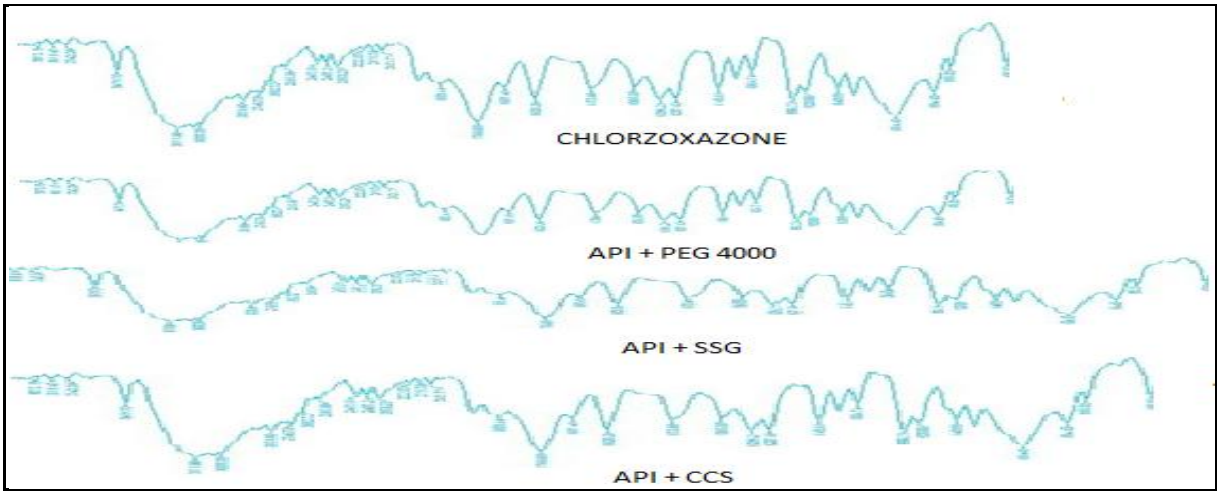

Fig. 2: FTIR Spectra of API & Physical Mixtures (Drug+ PEG4000/SSG/CCS)

Table 5: FTIR Spectrum data of Physical Mixtures (Drug+ PEG4000/SSG/CCS)

Sr. no.	Functional Group	Standard Range of wave number (cm^{-1})	Observed Peaks at wave number (cm^{-1}) PM PEG4000	Observed Peaks at wave number (cm^{-1}) PM SSG	Observed Peaks at wave number (cm^{-1}) PM CCS
1	N-H	3000 - 3700	3150.46	3148.54	3154.98
2	C = O	1600 – 1900	1615.83	1602.43	1640.23
3	C = C	1450 – 1600	1474.41	1470.94	1479.53
4	C –N	1020 – 1230	1147.67	1138.04	1140.32
5	C- O	900 - 1300	959.32	933.32	993.23
6	C - C	800 - 1200	801.03	800.01	802.32
7	C - Cl	600 - 800	734.00	730.93	739.29

Differential Scanning Calorimetry (DSC) (23)

The Differential Scanning Calorimetry (DSC) technique was used for determination of melting point of API. The melting point was found to be 194.53- 198.82^{0}C. DSC Spectra of an API is as shown in Fig.3

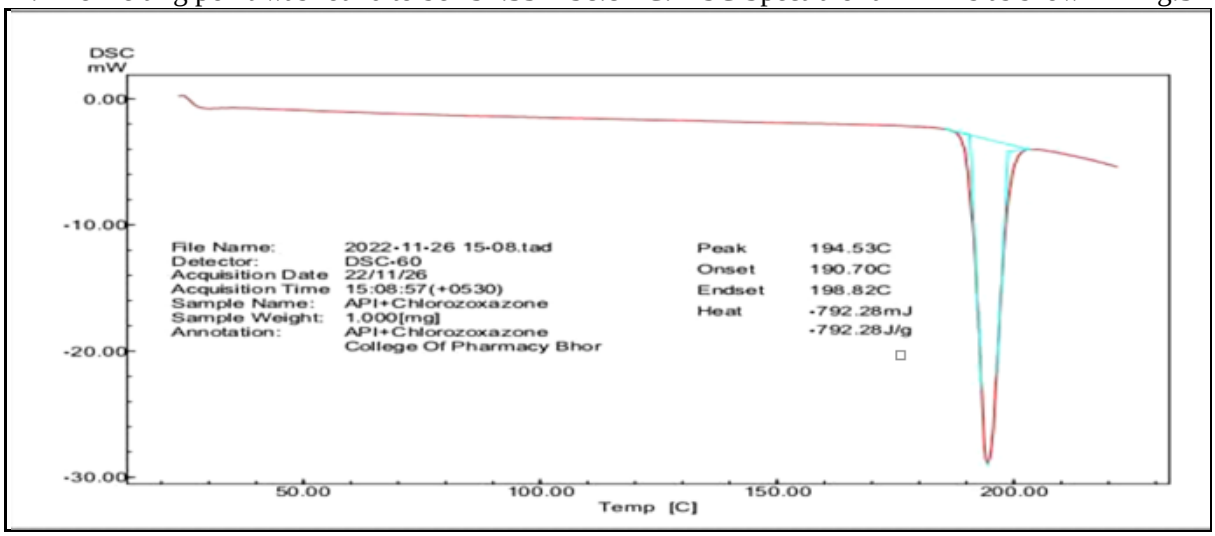

Fig. 3: DSC Spectra of an API

Determination of Calibration Curve of API (24)

The calibration curve of API was determined spectrophotometrically in 0.1N HCl at 244 nm. The calibration curve was plotted between concentration and absorbance in concentration range 2-10 µg/ml. The graphical presentation of Calibration curve is as shown in Fig. 4 Tabular presentation of Calibration data is as shown in Table 6

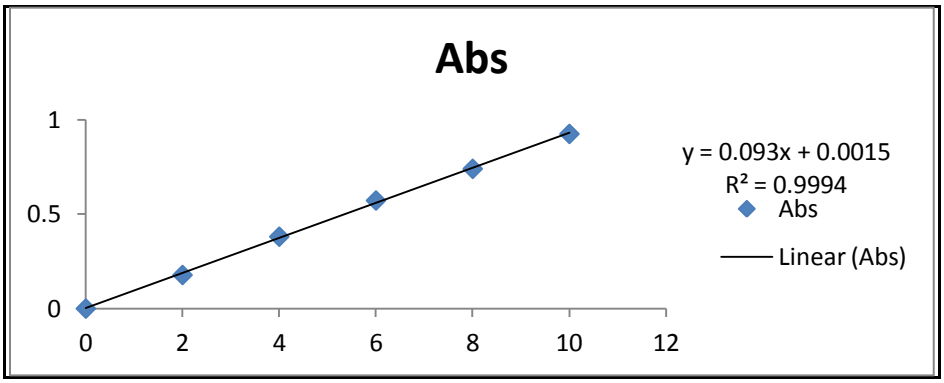

Fig. 4: Standard calibration curve of Chlorzoxazone in 0.1 N HCl

Table 6: Tabular presentation of Calibration data

Concentration	Absorbance
0	0
2	0.1779
4	0.3809
6	0.5727
8	0.7406
10	0.9255

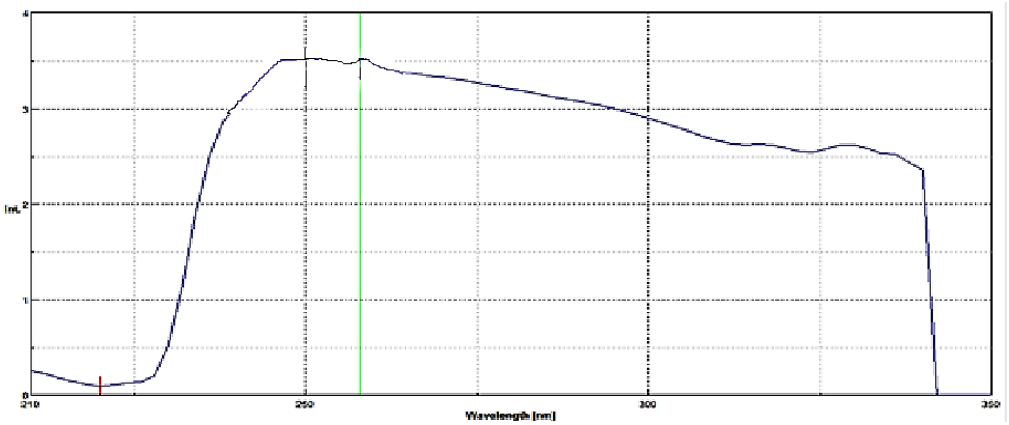

Fig. 5: λ max determination of API

Formulation of Solid Dispersion of an API by Kneading Method:

The Solid Dispersion of an API was formulated with PEG4000 in different ratio using Water: Ethanol (1:1) as a solvent by using kneading method as shown in Table 1

Evaluation Parameters for Solid Dispersion (25)

***Determination of Percentage yield, Saturation Solubility, XRD and FT-IR spectra of Solid* dispersion:**

Percentage yield- The percentage yield of different ratios of solid dispersion was found to be in range 99.5±0.30 to 98.2±0.40% as shown in Table 7

Table 7: Percentage Yield of Solid Dispersion

API : PEG 4000 Ratio	Percentage Yield of Solid Dispersion
1:1	**99.5±0.30**
1:2	99±0.40
1:3	99.2±0.52
1:4	98.2±0.40

Saturation Solubility Studies of Solid Dispersion (26)

Saturation Solubility Studies of API was compared with that of Solid Dispersion and the results are as shown in Table 8

Table 8: Saturation Solubility Data of API &Solid Dispersions

Pure Drug/ Formulation	Saturation Solubility in Water	Saturation Solubility in 0.1N HCl	Saturation Solubility in pH 6.8
Pure Drug	0.031±0.1	0.041±0.2	0.037±0.01
1: 1	**0.56±0.02**	**0.87±0.01**	**0.69±0.03**
1: 2	0.45±0.01	0.66±0.03	0.39±0.01
1: 3	0.36±0.03	0.49±0.02	0.38±0.01
1 : 4	0.24±0.02	0.33±0.01	0.22±0.03

**** All saturation solubility values are in µg/m***

X-Ray Diffraction studies of Solid Dispersion (27)

XRD Spectra of an API and Solid Dispersion (1:1) are as shown in Fig. 6 and Fig. 7 respectively. The XRD spectra of an API shows intense peaks which is attributed to crystalline structure of an API. While reduction in the peak intensity was observed in a solid dispersion. This may be attributed to partial amorphization of an API or enhancement of hydrophilicity of an API in presence of a hydrophilic carrier.

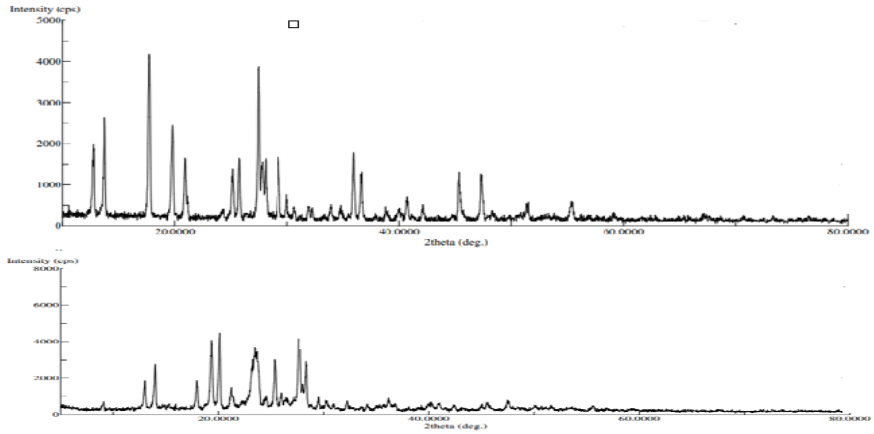

Fig. 6: XRD of Chlorzoxazone & Fig. 7: XRD of SD

Pre- Compression Evaluation Parameters (28)

Prior to Direct Compression, the powder blend was evaluated for Pre-compression parameters viz. Angle of Repose, Bulk Density, Tapped density, Carr's Index and Hausner's ratio, the results are as shown in following Table 9

Table 9:Pre-Compression Evaluation Parameters

Parameter	F1	F2	F3	F4	F5	F6	F7	F8	F9
Bulk density (gm/ml)	1.18±0.3	1.11±0.3	1.26±0.2	1.13±0.1	1.34±0.1	1.15±0.2	1.23±0.4	1.09±0.1	1.37±0.3
Tapped density (mg/ml)	1.5±0.3	1.41±0.3	1.6±0.3	1.44±0.2	1.71±0.2	1.47±0.1	1.56±0.3	1.38±0.3	1.74±0.1
Angle of Repose(θ)	29.7±1.1	27.7±0.7	32.8±1.6	29.7±0.8	29.0±1.0	31.2±.1.4	27.7±1.3	29.7±1.6	29.7±1.0
Carr's index (%)	19.3±1.1	17.2±0.8	21.9±1.0	18.8±1.0	24.6±0.9	19.8±1.0	22.6±0.9	16.8±0.9	25.3±0.9
Hausner's ratio	1.27±0.2	1.27±0.2	1.27±0.2	1.28±0.1	1.28±0.1	1.28±0.1	12.7±0.1	12.7±0.1	12.7±0.1

Post- Compression Evaluation Parameters (29)

The immediate release tablets of solid dispersion of an API (1:1 ratio) were formulated by direct compression technique. The tablets were evaluated for post compression parameters viz. Tablet Appearance, Weight Variation, Thickness, Hardness, Friability, Drug Content, Disintegration Test, Water Absorption Ratio, Uniformity of dispersion, *In-vitro* Dissolution Test and Stability Studies. The results for post compression parameters as are as follows:-

Table 10: Post-Compression of Immediate release tablet

Parameters ±SD	F1	F2	F3	F4	F5	F6	F7	F8	F9
Appearance	**White, Oval shaped tablets with smooth texture**								
Weight Variation (mg)	592±3.51	**601±1.00**	605±4.58	590±3.51	595±3.7	597±3.60	603±3.21	598±3.21	599±1.52
Thickness (mm)	4.02±0.24	**4.06±0.15**	4.01±0.22	4.05±0.22	4.05±0.25	4.05±0.26	4.06±0.23	4.05±0.21	4.05±0.22
Hardness (kg/cm^2)	4.2±0.77	**3±1.04**	4.1±1.09	4.3±1.01	6±0.57	4±1.00	4±1.52	4±0.55	3±1.01
%Friability	0.82±0.01	**0.67±0.01**	0.94±0.03	0.85±0.03	0.55±0.04	0.78±0.02	0.87±0.03	0.73±0.02	0.78±0.02
Drug content	99.3±0.76	**99.3±0.76**	99.3±0.76	99.3±0.76	99.3±0.76	99.3±0.76	99.3±0.76	99.3±0.76	99.3±0.76
Disintegration	7.55±1.00	**7.55±1.00**	7.55±1.00	7.55±1.00	7.55±1.00	7.55±1.00	7.55±1.00	7.55±1.00	7.55±1.00
Water absorption ratio	44.6±0.67	**44.6±0.67**	44.6±0.67	44.6±0.67	44.6±0.67	44.6±0.67	44.6±0.67	44.6±0.67	44.6±0.67
Uniformity of dispersion	Passable	**Passable**	Passable	Passable	Passable	Passable	Passable	Passable	Passable

**** All values are ±SD***

The F2 batch has shown better results for post compression evaluation, hence considered as optimized batch.

In-vitro Dissolution Test (30)

In-vitro Dissolution Test was carried out by using USP Type II Dissolution Apparatus (paddle type), 900 ml of 0.1 N HCl as dissolution medium, at a speed of 50 rpm at temperature 37±0.5^{o}C. *In-vitro* drug release data for all the solid dispersion 4 batches is as shown in Table 11 as follows:-

Table 11: *In-vitro* drug release of Solid dispersion

Time	Pure drug	1:1	1:2	1:3	1:4
0	0	**0**	0	0	0
5	6.11	**14.54**	12.89	10.21	9.23
10	10.43	**25.54**	22.32	16.65	14.45
15	18.63	**40.65**	35.56	29.89	26.64
20	22.32	**51.65**	47.54	42.44	31.32
25	26.21	**63.67**	56.42	48.22	36.33
30	30.24	**75.21**	63.85	55.34	41.38

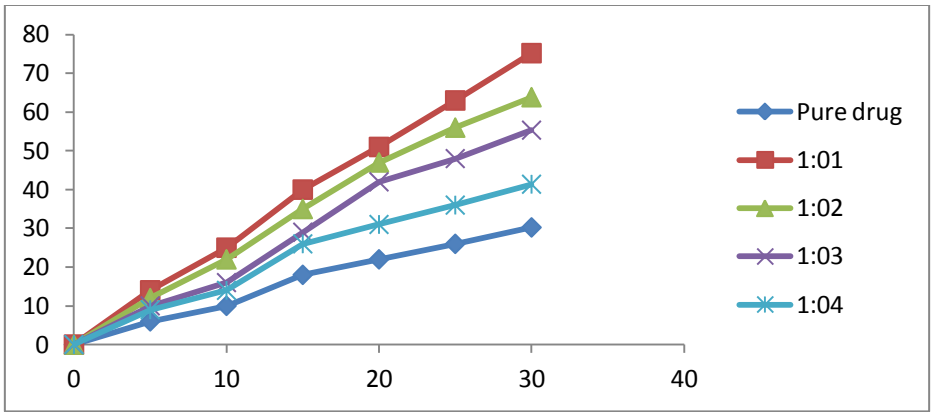

Fig. 8: *In-vitro* drug release of pure drug and Solid Dispersion batches

In-vitro Dissolution Test was carried out by using USP Type II Dissolution Apparatus (paddle type), 900 ml of 0.1 N HCl as dissolution medium, at a speed of 50 rpm at temperature37±0.5^{o}C. **F2 batch** has shown maximum *In-vitro* drug release. *In-vitro* drug release data for all the 9 batches is as shown in Table 12 as follows:-

Table 12: *In-vitro* drug release of Immediate Release Tablets

Time	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	**0**	0	0	0	0	0	0	0
5	40.01	**52.94**	44.21	45.86	46.32	47.54	49.65	50.11	51.44
10	53.64	**62.99**	51.12	57.32	57.91	58.53	58.89	59.63	61.95
15	62.67	**71.42**	61.99	66.98	68.99	69.1	69.79	69.87	70.97
20	70.44	**80.11**	72.19	74.15	77.34	78.1	79.22	79.39	79.99
25	80.12	**90.96**	83.33	87.17	87.99	88.1	88.30	89.12	89.96
30	90.14	**97.23**	91.38	93.24	94.86	94.1	94.32	95.11	96.42

Graphical presentation of *In-vitro* drug release data for all the 9 batches shown in Fig. 9 and Fig. 10

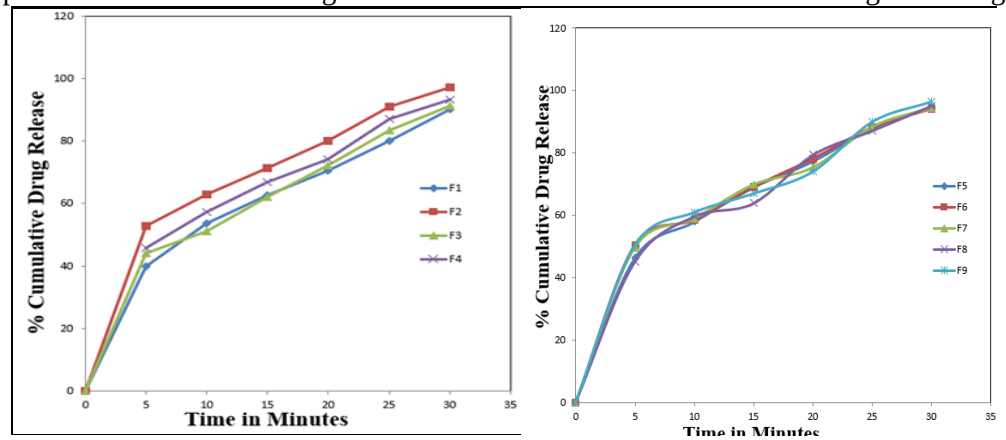

Fig. 9: *In-vitro* drug release of F1 to F4 batches and Fig. 10: *In-vitro* drug release of F5 to F9 batches

The F2 batch has shown maximum drug release of 97.23% in 30 minutes, hence considered as optimized batch amongst all F9 batches. The individual drug release patterns of all batches are as shown in the following graphs and figures. The *In-vitro* dissolution profiles of pure drug, SD1:1 and an optimized batch (F2) were compared and the results are as shown in Table 13 and Fig.11.

Table 13: *In vitro* dissolution profiles of pure drug, SD1:1 and batch (F2)

Time (min)	% Cumulative Drug Release		
	Pure Drug	SD1:1	F2
0	0	0	0
5	6.76	14.70	52.94
10	10.11	25.76	62.99
15	18.83	40.34	71.42
20	22.32	51.87	80.11
25	26.29	63.19	90.96
30	30.21	58.28	97.23

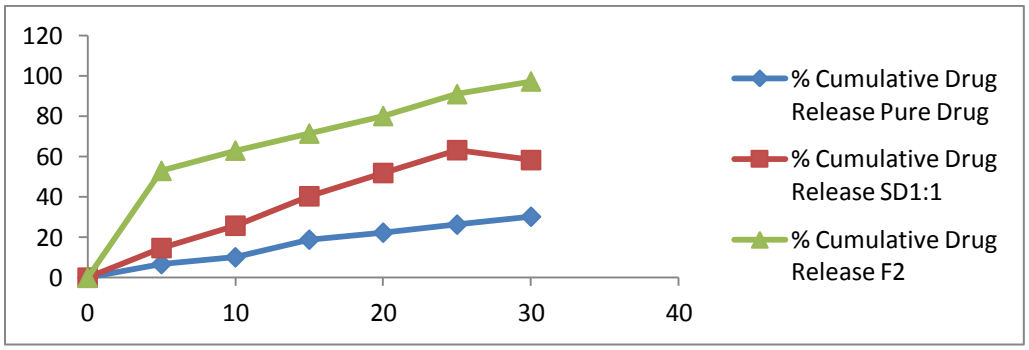

Fig. 11: *In-vitro* drug release of pure drug, SD 1:1 & F2 batch.

Stability Studies:

Stability studies of optimized formulation batch F2 was carried out over a period of 90 days at room temperature and at 40±2ºC/75% RH & results stated no significant changes in hardness, disintegration time, drug release pattern and drug content were observed. Hence formulation has found to be stable. The results for Stability Studies are as shown in Table 14

Table 14: Stability Studies of Optimized Batch F2

Storage Condition	INTIAL (0)			
	Hardness (kg/cm^2)	**Disintegration time (min)**	**Drug content (%)**	***In-vitro* drug release (%)**
RT	6±0.57	6.01±0.72	99.86±0.15	97.23
40±2ºC/75% RH	6±0.42	6.46±1.21	99.84±0.13	96.58
	30 Days			
RT	6±0.33	6.56±1.32	99.80±0.10	96.57
40±2ºC/75% RH	6±0.30	6.51±0.54	99.74±0.03	96.45
	60 Days			
RT	6±0.77	6.02±0.72	99.86±0.15	97.03
40±2ºC/75% RH	6±0.62	6.48±1.21	99.82±0.13	99.58
	90 Days			
RT	6±0.33	6.56±1.32	99.80±0.10	96.57
40±2ºC/75% RH	6±0.30	6.51±0.54	99.74±0.03	96.45

Conclusion

From the research work carried out, it can be concluded that solubility of Chlorzoxazone can be enhanced by Solid dispersion technique, by using PEG 4000 as a carrier. The enhanced solubility rate of Chlorzoxazone in solid dispersion may be attributed to the solubilization effect of PEG 4000. Instrumental analysis can be used effectively in formulation and development of dosage form. This is concluded with reference to FT-IR a study which has confirmed no interactions between API and excipients, DSC has confirmed melting point of an API, and XRD studies confirmed partial amorphization of an API from crystalline to amorphous form in solid dispersion. Superdisintegrants has always proven to play an important role in formulation of immediate release tablet. Superdisintegrants SSG and CCS have improved disintegration and dissolution characteristics of an API. Solubility of an API was enhanced by 18.064 folds as compared to pure drug. Hence from the results obtained of F2 batch, it can be concluded that the aim and objectives of current research work has been successfully accomplished.

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Conflict of Interest

The writers stated that they had no conflicts of interest.

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