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Research Article

Advancement and Characterization of Solid Dispersion Containing The Low Water Soluble Anti-HIV Drug

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Abstract

Pharmacological efficiency of a functioning moiety influences the portion to direct, openness of active moiety at its receptor site and measure the quantity of active moiety for do the pharmacological impact. This kind of active structure is referred to as physiological organization capacity, Systematic administration ability or just bioavailability. For the inconstancy of medication, pharmacological result is connected with noticed restorative levels. Bioavailability is consequence of speed and extents (amount) of assimilation of substance moiety don't alteration with connection to its portion sort. It is depicted as outcomes of the speed and amount of active moiety and excipients consumed from the sort of completed portion and arrive at the situating of the activity. The low bioavailability is shown as poor solubilization in watery media, a low release of active part in biological fluids, flimsiness of active part in the natural media, less infiltration from the natural membrane, associate initial Intensive metabolism.

According to the BCS classifications drugs like Elvitegravir which has a place with class II have the less solvency and great penetrability. Thus, it turns into a critical challenge for a formulator, to plan these medications having the inconsistent or non-uniform medication discharge profile, drug assimilation influenced by the food, and from one patient to another and non-uniform bioavailability all through the GIT.

Keywords: Bioavailability, Solid Dispersion, Water solubility, Drug Release

Introduction

For enhancement of solubility of poorly water soluble drug various techniques were used. Fong et al.; (2016) deliberate dispersion by layophilization technique. In this technique they used the drug of the category of COX – 2

inhibitor like Celecoxeb. These drugs go very limitedly in the aq. media. There are number of studies and literatures are available which claims the solubility enhancement of this active molecule but there is not a single appropriate justification available behind the reason of solubility enhancement. Fong used the Phospholipids (PL) as a carrier. Shergill et al. (2016) deliberate a modified release formulation of Disulfiram. This drug gets metabolized or degrades at the lower pH. To enhance the drug bioavailability it was required to shield the active molecule from acidic environment. Hence in this experiment four types of polymers were used. Two polymers i.e. Kolliphor(®) P 188 and P 237 were utilized in dispersion process for add up the solubliztion of drug. While other two polymers i.e. Kollidon(®) SR and HPMC were utilized for protecting the active molecule from acidic environment along with giving a sustained release property. Pekamwar S. S et al. (2015) deliberate a dispersion of API with a carrier named as Soluplus. The object of this experiment was to add up the Solublization characteristics of the API i.e. Lopinavir (LVR). This drug has very narrow solvation in the aq. media. Polymer was used with the API in different quantity. Salmani et al. (2015) deliberate a final product of an antihypertensive drug. In the study dispersion was manufactured for the API i.e. Atorvastatin. The intention of this research was to convalesce the bioavailability of this active molecule by improving amorphous disposition of API after making dispersion. In the manufacturing Eudragit polymer was used as carrier. Al-Hamidi et al. (2015) deliberate a dispersion of API in association with a carrier named as amino sugars. The object of this research was to add up the Solublization qualities of the API i.e. Piroxicam. Prabhu et al. (2015) deliberate a dispersion of API in association with a carrier known as VBP-1. This is a newer kind of carrier which comes under the category of Organosulphur. The object of this research was to add up the Solublization qualities of the API i.e. Atorvastatin calcium. Raval et al. (2015) deliberate a dispersion of API with the multiple carriers. The intention of this research was to add up the Solublization properties of the API i.e. Chlorzoxazone. Akbari et al. (2015) deliberate a dispersion of API along with the carrier named as Polygols (PEG). The object of this research was to add up the Solublization properties of the API i.e. Spironolactone. This drug has very narrow solvation in the aq. fluid. Polymer was used with the API in different quantity. In the study hot melt technique was used.

Other solid formulations are like SD of Povidone & reserpine (Stupak EI. et al; 1972), SD of PEG & tolbutamide (Kaur R. et al; 1980), SD of PEG & chloramphenicolurea(Sekiguchi K. et al; 1964). SD of Ac di sol, crosspovidone & Etoricoxib (Prameela R. et al; 2008), SD of Povidone, crosspovidone & Aceclofenac (Thiyagarajan A. et al; 2009)

MATERIALS AND METHODS

Elvitegravir was received as gift sample from M/s Eli Lilly and Company India, Hypromellose and Klucel from M/s Arihant Pharma, PVP from M/s BASF, SMC from M/s JRS Pharma, SSG and Polyplasdone XL 10 from M/s Natco Pharma and Ac-Di-Sol from M/s FMC biopolymers.

Manufacturing by use of Water Soluble agents

Hypromellose, PVP (Povidone) and Klucel (Hydroxypropyl Cellulose) were added with API using methanol as a solvent in common solvent method.

Elvitegravir and carrier used in multiple ratio for the manufacturing of Dispersion.

API & drug carrier were dispensed and solubilized in the SS container using methanol as a solvent. Continuously stirred

the dispersion under vacuum. At the temp. of approx 65°C solvent was evaporate. A solid mass was obtained and converted in to fine powder form.

Manufacturing by use of Water dispersible agents

SMC, Sod. Starch Glycolate (SSG), Polyplasdone XL 10 and Ac-Di-Sol mixed with API using methanol as a solvent, in solvent evaporation method.

Elvitegravir and carrier utilized in multiple ratio and amount of the excepients for the manufacturing of Dispersion.

Dispensed qty of API was solubilized in the SS container using methanol as a solvent. A clear solution was obtained. In this water dispersible carrier was transferred. Mixture was constantly stirred for two hours under low pressure and at the temp. of approx 65°C to obtain a dry form. This dried mixture was further dried at 60°C to remove the remainder of the solvent. A solid mass was obtained and converted in to fine powder form.

Drug Content

In the 100 ml SS container 0.1 gm of Mixture was extracted with 80 ml of Methyl Alcohol. These solutions were shaked vigorously to extract out the API, then filtered. After filtration and dilution with N/10 HCl, these are scanned in spectrophotometer at the λ of 313 nm.

Drug Release

Drug release of Elvitegravir was studied in Elecrolab Dissolution Equipment. For the dissolution following parameters were kept

Apparatus: USP Type II (Paddle)

Media: N/10 hydrochloric acid

Volume: 0.9 Litre RPM: 50

Temperature of Media: 37°C ± 1°C

Sample Volume: 5 ml

Amount of Dispersion mixture having the Elvitegravir corresponding to 0.1 gm was transferred in the each basket of Dissolution Equipment. At the defined time interval sample quantity taken and treated with the dissolution media. After proper dilution and treatment the sample was run in the spectroscopy at the λ of 313 nm. Quantification of drug amount in the sample was carried using standard curve. The whole process was performed three times (n=3).

XRD

For different qty of dispersion the XRD evaluated employing FC – Ka radiation. In form of 2θ angle, the diffractograms were analyzed at 2.4°/ min.

FT-IR Spectra

For different qty of dispersion the FT-IR spectra were also measured using FTIR spectrophotometer (M/s SHIMADZU) and KBr disc as a reference.

DSC

For different qty of dispersion the DSC thermograms evaluated using Differential Scanning Calorimetry (M/s Mettler). Samples were treated at 10^0C per min for the range 20^0 – 140^0C in aluminium Crucibles.

Table 1: Manufacturing Formula of Different Dispersions

S.No.	Trial No.	Ratio	API	Carrier
1.0	D 1	9.5 : 0.5	Elvitegravir	Hypromellose
2.0	D 2	9 : 1		
3.0	D 3	8 : 2		
4.0	D 4	9.5 : 0.5	Elvitegravir	PVP

5.0	D 5	9 : 1		
6.0	D 6	8 : 2		
7.0	D 7	9.5 : 0.5	Elvitegravir	Klucel
8.0	D 8	9 : 1		
9.0	D 9	8 : 2		
10.0	D 10	3 : 1	Elvitegravir	SMC
11.0	D 11	1 : 1		
12.0	D 12	1 : 2		
13.0	D 13	3 : 1	Elvitegravir	SSG
14.0	D 14	1 : 1		
15.0	D 15	1 : 2		
16.0	D 16	3 : 1	Elvitegravir	PPL- XL10
17.0	D 17	1 : 1		
18.0	D 18	1 : 2		
19.0	D 19	3 : 1	Elvitegravir	Ac-Di-Sol
20.0	D 20	1 : 1		
21.0	D 21	1 : 2		

RESULTS

Drug Content

Both types of dispersions were observed to be free flowing powder. Amount of Elvitegravir in the dispersion was measured utilizing spectrophotometer and observed to be satisfactory. According the data drug was homogenously mixed in the solid dispersion.

Table 2: Drug Content in solid dispersion

S No.	D 1	D 2	D 3	D 4	D 5	D 6	D 7	D 8	D 9	D 10	D 11	D 12	D 13	D 14	D 15	D 16	D 17	D 18	D 19	D 20	D 21
1	94.7 mg	89.6 mg	79.5 mg	94.5 mg	90.2 mg	78.5 mg	94.1 mg	89.1 mg	80.6 mg	74.9 mg	48.7 mg	32.8 mg	74.9 mg	49.5 mg	33.4 mg	74.7 mg	49.7 mg	33.2 mg	74.7 mg	49.7 mg	31.9 mg
2	94.6 mg	89.4 mg	80.4 mg	94.6 mg	88.8 mg	80.0 mg	94.7 mg	89.5 mg	79.8 mg	74.8 mg	49.2 mg	31.7 mg	74.7 mg	49.4 mg	33.1 mg	74.8 mg	49.1 mg	32.5 mg	74.1 mg	49.1 mg	32.0 mg
3	94.7 mg	89.4 mg	80.3 mg	94.5 mg	89.5 mg	79.6 mg	94.6 mg	89.4 mg	80.0 mg	74.2 mg	48.9 mg	32.5 mg	74.7 mg	49.7 mg	33.5 mg	74.3 mg	49.9 mg	33.6 mg	74.5 mg	49.4 mg	32.4 mg
4	94.6 mg	89.5 mg	80.0 mg	94.6 mg	89.5 mg	79.5 mg	94.6 mg	90.0 mg	80.2 mg	74.7 mg	49.0 mg	32.5 mg	74.8 mg	48.9 mg	32.9 mg	74.3 mg	49.4 mg	32.8 mg	74.3 mg	48.9 mg	31.8 mg
X	**94.7 mg**	**89.5 mg**	**80.1 mg**	**94.6 mg**	**89.5 mg**	**79.4 mg**	**94.5 mg**	**89.5 mg**	**80.2 mg**	**80.2 mg**	**74.7 mg**	**49.0 mg**	**32.4 mg**	**74.8 mg**	**49.4 mg**	**33.2 mg**	**74.5 mg**	**49.5 mg**	**33.0 mg**	**74.4 mg**	**49.3 mg**
SD	**0.06**	**0.1**	**0.4**	**0.06**	**0.57**	**0.64**	**0.27**	**0.37**	**0.34**	**0.34**	**0.31**	**0.21**	**0.47**	**0.1**	**0.34**	**0.28**	**0.26**	**0.35**	**0.48**	**0.26**	**0.35**
CV	**0.06**	**0.11**	**0.5**	**0.06**	**0.64**	**0.8**	**0.29**	**0.42**	**0.43**	**0.43**	**0.42**	**0.43**	**1.46**	**0.13**	**0.69**	**0.83**	**0.35**	**0.71**	**1.45**	**0.35**	**0.71**

Drug Release

As per the observation, from the dispersion, release of Elvitegravir was greater than the release of untreated API. As per the results dispersion of Elvitegravir follows the first order kinetics. Release from dispersions was observed to be superior to the release of API as such. Solid dispersion with Povidone gives much higher release in contrast to release with the dispersion of Hypromellose & Klucel.

As the qty. of polymer increases from 5% to 10% the release also increases. However, at the polymer amount of 20% drug dissolution get reduced, may be due to the aggregation of particles. Hence, the polymer quantity of 10% was observed to be satisfactory for enhancing the release with aqueous soluble polymers. The order of water soluble polymer for enhancing the release was Povidone (PVP) > Klucel > Hypromellose.

Among the different polymers, Water insoluble polymers have the significant impact on the release. Polyplasdone XL 10 and Ac-di-sol in the ratio of 1:1 with the Elvitegravir have the major impact on release by enhancing the release by 28.15 and 47.24 fold. The order of water dispersible polymer for enhancing the release was Ac-Di-Sol > Polyplasdone XL 10 > SSG >SMC.

As the qty. of Superdisintegrants increases from 25% to 50% the release also increases. However, at the polymer amount of 66% drug release remain unaffected.

Hence, the polymer quantity of 50% was observed to be satisfactory for enhancing the release with water dispersible polymers. Among the different carriers the order enhancing the release was Ac-Di-Sol > Polyplasdone XL 10 > Povidone (PVP) > Klucel > SSG > SMC > Hypromellose.

Table 3: Percentage Release from the Dispersions of Water Soluble Agents

% Drug (x ± s.d.) (n=3)										
Time	**Elvitegravir**	**D 1**	**D 2**	**D 3**	**D 4**	**D 5**	**D 6**	**D 7**	**D 8**	**D 9**
5 min	18.21 % ± 1.08	26.85 % ± 1.05	26.38 % ± 1.54	23.4 % ± 1.08	41.96 % ± 1.55	75.82 % ± 1.42	68.72 % ± 1.22	70.95 % ± 1.52	85.44 % ± 1.16	69.82 % ± 1.12
10 min	21.55 % ± 1.21	28.84 % ± 1.42	36.26 % ± 1.08	28.8 % ± 1.22	47.92 % ± 1.15	84.4 % ± 1.18	78.46 % ± 1.18	75.34 % ± 1.08	88.25 % ± 1.68	72.28 % ± 1.69
20 min	26.44 % ± 1.08	34.45 % ± 1.15	45.95 % ± 1.16	38.5 % ± 1.85	55.35 % ± 1.42	91.95 % ± 1.75	88.53 % ± 1.45	79.32 % ± 1.16	90.84 % ± 1.25	76.05 % ± 1.45
30 min	29.24 % ± 1.21	39.38 % ± 1.15	51.26 % ± 1.51	49.32 % ± 1.48	61.08 % ± 1.24	94.27 % ± 1.16	97.94 % ± 1.41	82.61 % ± 1.54	94.15 % ± 1.71	78.05 %± 1.15

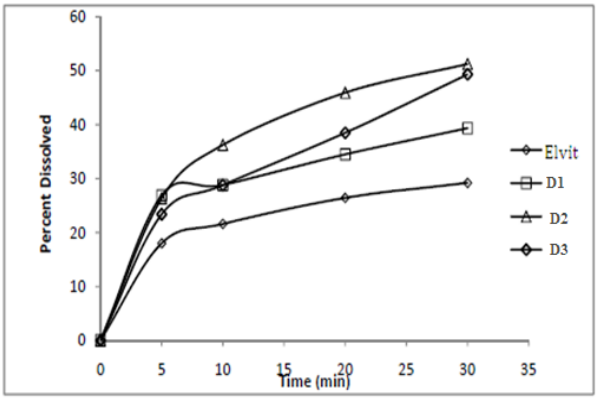

Fig 1.0: Release of Elvitegravir -Hypromellose Dispersions

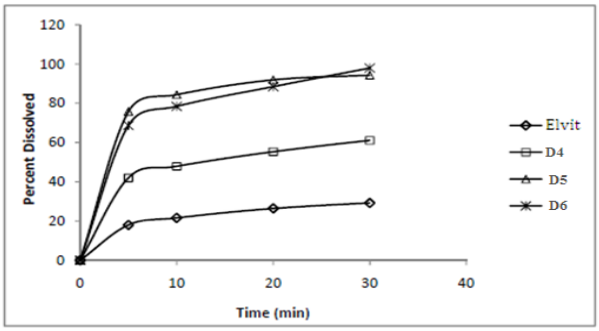

Fig. 2.0: Release of Elvitegravir -PVP Dispersions

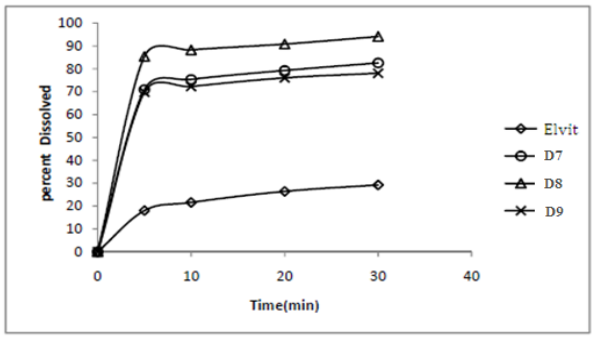

Fig. 3.0: Release of Elvitegravir -Klucel Dispersions

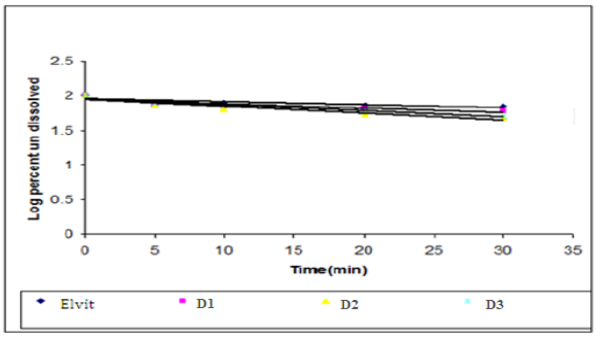

Fig. 4.0: Logarithmic Release of Elvitegravir and its Dispersions in Water Soluble Agent (Hypromellose)

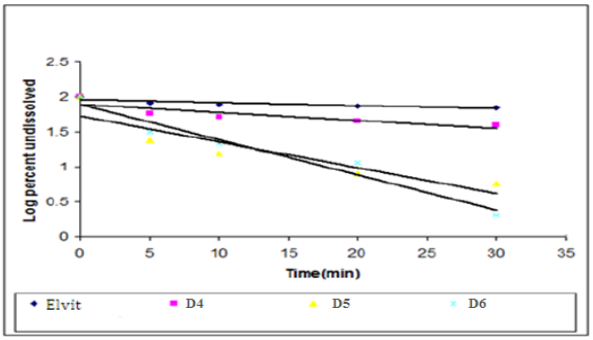

Fig. 5.0 : Logarithmic Release of Elvitegravir and its Dispersions in Water Soluble Agent (PVP)

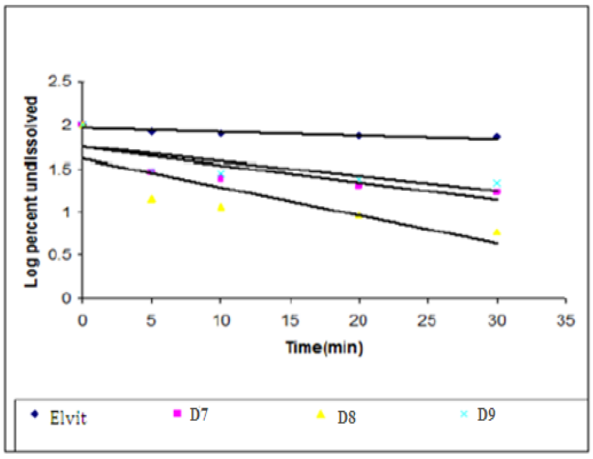

Fig. 6.0: Logarithmic Release of Elvitegravir and its Dispersions in Water Soluble Agent (Klucel)

Table 4: Release from the Dispersions of Water Dispersible Agents

Time	Elvitegravir	D 10	D 11	D 12	D 13	D 14	D 15	D 16	D 17	D 18	D 19	D 20	D 21
5 min	18.21 % + 1.08	78.31 % + 1.42	79.45 % ± 1.05	68.85 % ± 1.06	68.63 % ± 1.51	76.21 % ± 1.16	87.11 % ± 1.71	83.91 % ± 1.71	81.42 % ± 1.15	82.71 % ± 1.09	70.31 % ± 1.31	74.51 % ± 1.63	78.85 % ± 1.21
10 min	21.55 % + 1.21	80.45 % + 1.72	84.18 % ± 1.41	77.96 % ± 1.62	70.55 % ± 1.41	77.15 % ± 1.19	87.75 % ± 1.51	84.65 % ± 1.31	97.51 % ± 1.51	85.53 % ± 1.61	76.85 % ± 1.61	101.2 % ± 1.25	84.81 % ± 1.74
20 min	26.44 % + 1.08	84.61 % + 1.22	85.25 % ± 1.43	82.17 % ± 1.78	71.44 % ± 1.35	75.95 % ± 1.18	88.15 % ± 1.16	84.92 % ± 1.15	96.75 % ± 1.24	97.75 % ± 1.19	81.41 % ± 1.42	102.1 % ± 1.51	86.05 % ± 1.41
30 min	29.24 % + 1.21	86.4 % + 1.08	86.32 % ± 1.05	85.05 % ± 1.05	71.65 % ± 1.07	75.98 % ± 1.05	88.90 % ± 1.06	84.61 % ± 1.08	100.2 % ± 1.05	99.55 % ± 1.05	83.25 % ± 1.05	101.8 % ± 1.05	90.41 % ± 1.05

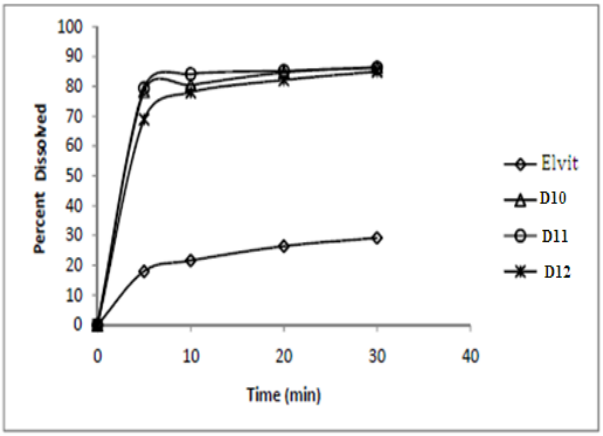

Fig. 7.0: Release of Elvitegravir -SMC Dispersions

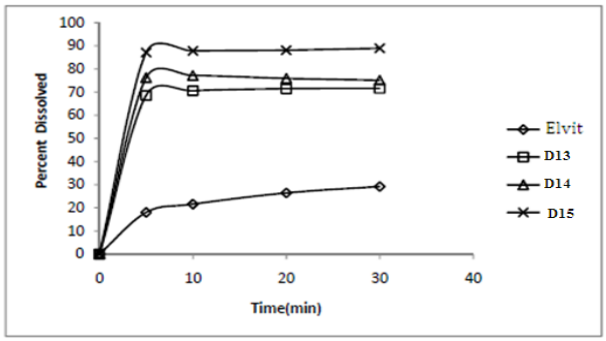

Fig. 8.0: Release of Elvitegravir -SSG Dispersions

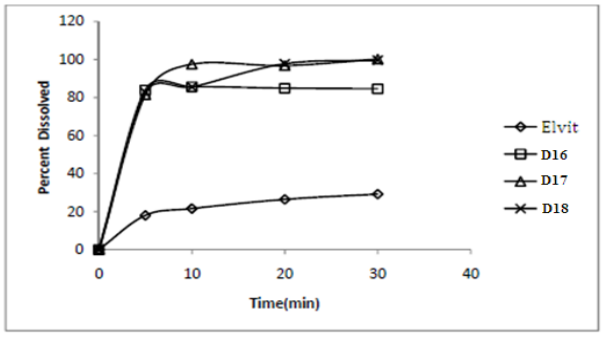

Fig. 9.0: Release of Elvitegravir –PPL-XL 10 Dispersions

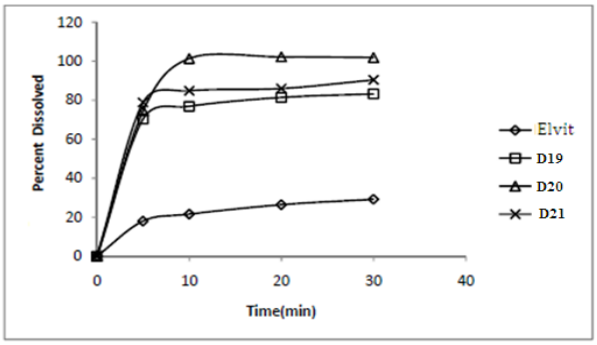

Fig. 10.0: Release of Elvitegravir –Ac-Di-Sol Dispersions

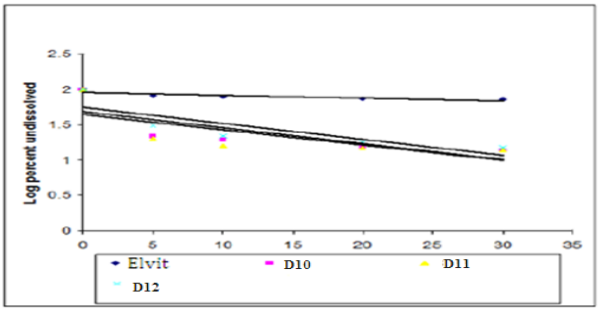

Fig. 11.0: Logarithmic Release of Elvitegravir and its Dispersions in Water Dispersible Agent (SMC)

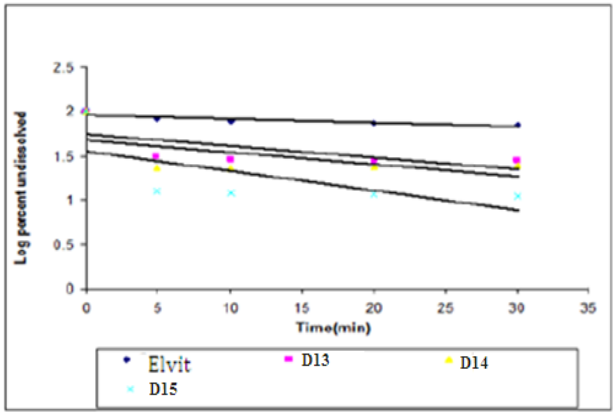

Fig. 12.0: Logarithmic Release of Elvitegravir and its Solid Dispersions in Water Dispersible Agent (SSG)

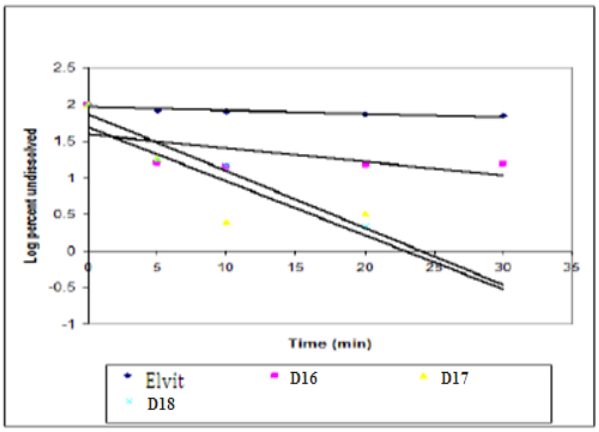

Fig. 13.0: Logarithmic Release of Elvitegravir and its Solid Dispersions in Water Dispersible Agent (PPL-XL 10)

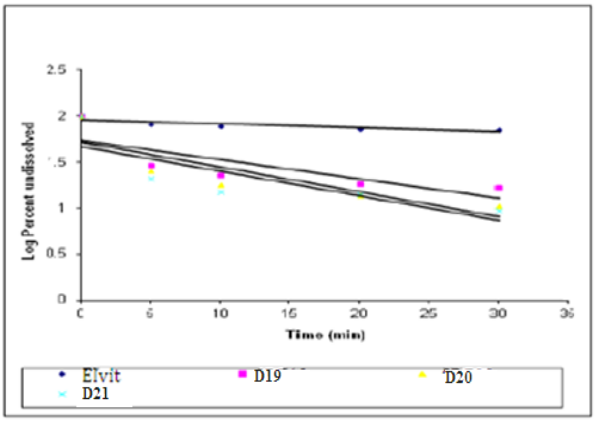

Fig. 14.0: Logarithmic Release of Elvitegravir and its Solid Dispersions in Water Dispersible Agent (Ac-Di-Sol)

Table 5: Values of (r) according to Zero order and First order Kinetics

Composition	r value	
	Zero order kinetics	First order kinetics
D 1	0.9971	0.9965
D 2	0.9381	0.9621
D 3	0.9991	0.9945
D 4	0.9814	0.9932
D 5	0.8831	0.9675
D 6	0.9785	0.9395
D 7	0.9584	0.9825
D 8	0.9815	0.9845
D 9	0.9705	0.9817
D 10	0.9662	0.9805
D 11	0.7405	0.7822
D 12	0.8413	0.9095
D 13	0.7415	0.7505
D 14	0.6241	0.6136
D 15	0.9562	0.9585
D 16	0.9803	0.9865
D 17	0.5705	0.8073
D 18	0.9154	0.9775
D 19	0.8673	0.9135
D 20	0.8372	0.9144
D 21	0.8755	0.9161

3.3 XRD

In the XRD of the API, multiple peaks are appeared which signify the crystallinity of Elvitegravir. While the dispersions have very less diffraction peaks or they get omitted, which indicates the amorphous property of the material. Hence the solublization of Elvitegravir increases in dispersion form.

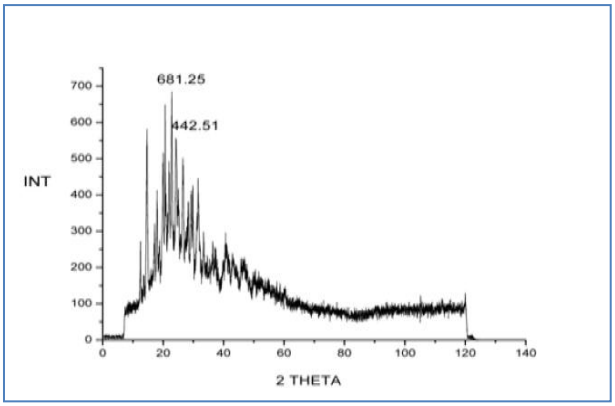

Fig. 15.0: XRD of Elvitegravir

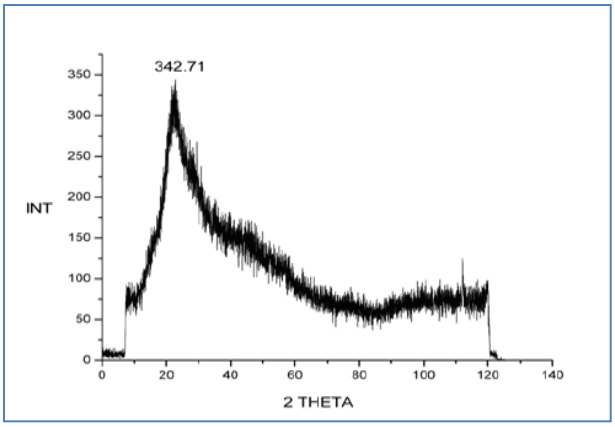

Fig. 16.0 : XRD of Elvitegravir -PVP (9: 1)

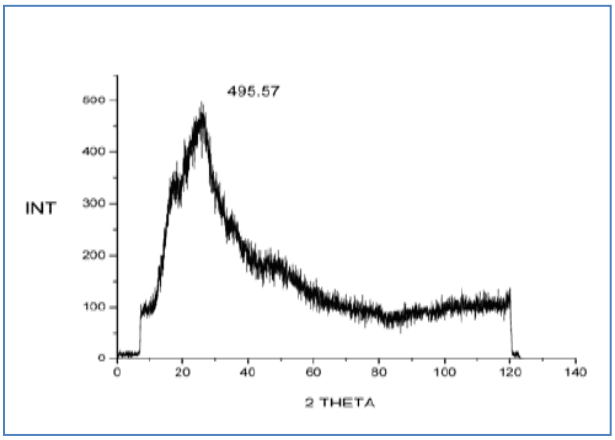

Fig. 17.0: XRD of Elvitegravir –Ac-Di-Sol (1: 1) SD

3.4 FTIR

Typical peaks of API are present in dispersions which show no incompatibility in Elvitegravir and different polymers.

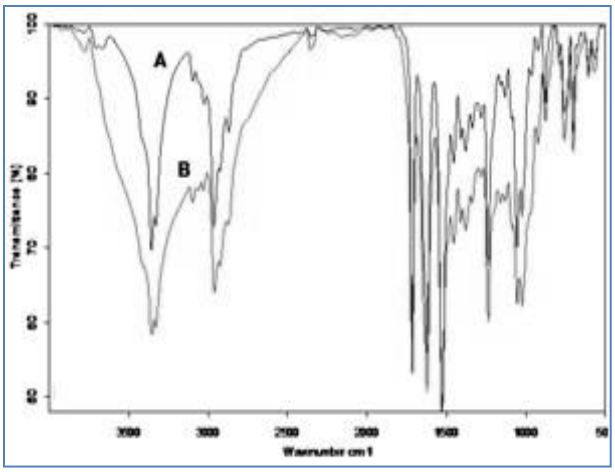

Fig. 18.0 : IR of (A) Elvitegravir and (B) Elvitegravir -PVP (9: 1)

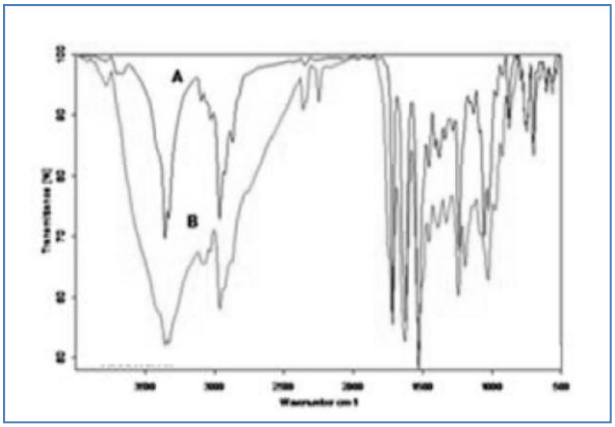

Fig. 19.0: IR of (A) Elvitegravir and (B) Elvitegravir – Ac-Di-Sol (1:1) SD

3.5 DSC

Characteristic melting peaks of API are present in dispersions which show no incompatibility in Elvitegravir and different polymers.

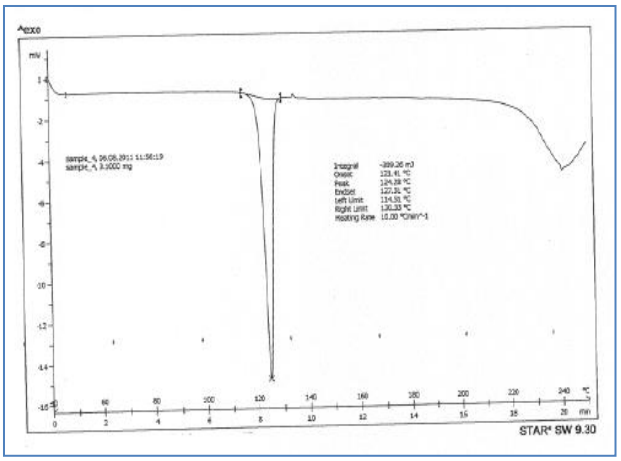

Fig. 20.0: DSC of Elvitegravir

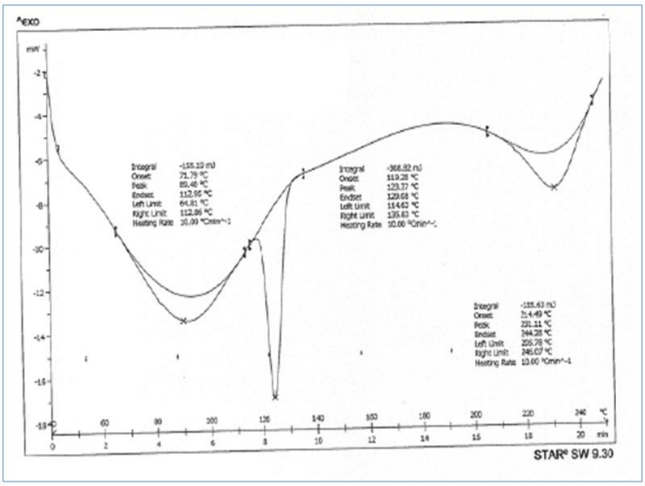

Fig. 21.0: DSC of Elvitegravir-PVP (9: 1)

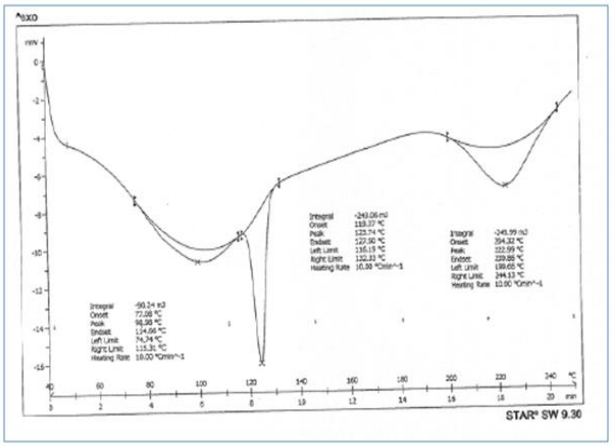

Fig. 22.0: DSC of Elvitegravir - Ac-Di-Sol (1: 1)

Conclusion

From the observed results following conclusions are made.

- The Drug release in dispersions enhances significantly.
- The order of water soluble agents for enhancing the release was Povidone (PVP) > Klucel > Hypromellose.
- The order of water dispersible agents for enhancing the release was Ac-Di-Sol > Polyplasdone XL 10 > SSG >SMC.
- There is no incompatibility in Elvitegravir and polymers as confirmed by FTIR & DSC.

In the dispersion, API gets transformed into amorphous molecular stage, confirmed by XRD.

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