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Preparation of Solid Dispersions of Poorly Soluble Drugs

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Abstract In order to ensure the optimum therapeutic effect of drug it is necessary to prepare the proper dosage form. Solubility is a significant physicochemical factor affecting absorption of drug and its therapeutic effectiveness. Poorly water soluble compounds have both solubility and dissolution related problems which can dramatically affect their bioavailability resulting in reduction of their therapeutic efficacy. To overcome such a problem solid dispersions of poorly soluble drugs like Cefixime, Valsartan and Ibuprofen were prepared and evaluated. Suitable carriers such as PVP K30 and HMPC etc. in different ratios were chosen. They were prepared by physical mixing and kneading method. The standard curves were prepared for cefixime, ibuprofen and valsartan in methanol. The release studies were carried out and compared. The results showed a marked increase in release of the drug from solid dispersions compared to the drug in its pure form. The percentage of the drug released for Ibuprofen increased from 12.78 to 52.4% (1:1 ratio), 70.2% (1:2 ratio) and 68.2% (1:3 ratio). The use of cefixime with hydroxypropymethylcellulose (HPMC) greatly improved the solubility of the drug and enhanced its dissolution rate. The percentage of the drug released increased from 13.2 to 31.4% (1:1 ratio), 34.9% (1:2 ratio) and 43.9% (1:3 ratio). The ratios which showed the best release were considered as the optimized formulations.

Keywords Solid dispersions, Carriers, Solubility, Optimized formulation, Release

Introduction

In order to ensure the optimum therapeutic effect of drug it is necessary to prepare the proper dosage form. To formulate an effective dosage form the drug must possess some important characteristics and one of them is the solubility in water. Since only dissolved drug can pass the gastrointestinal membrane, dissolution affects the systemic absorption.

Solubility is a significant physicochemical factor affecting absorption of drug and its therapeutic effectiveness. Poorly water soluble compounds have both solubility and dissolution related problems which can dramatically affect their bioavailability resulting in reduction of their therapeutic efficacy. One of the methods used to overcome such a problem was by preparing solid dispersions of those poorly soluble drugs. This technology depends on producing a complex using at least two parts generally a hydrophilic matrix and the hydrophobic drug intended to be formulated. The aim of the study was to prepare solid dispersions of poorly soluble drugs and evaluate them. Cefixime, Valsartan and Ibuprofen are poorly soluble drugs and thus methods to prepare solid dispersions of them were obtained. Moreover, suitable carriers in different ratios were chosen such as; PVP K30 and HMPC etc. Solid dispersions were prepared by physical mixing and kneading method. The standard curves were prepared for cefixime, ibuprofen and valsartan in methanol. The release studies were carried out and compared. The results showed a marked increase in release of the drug from solid dispersions compared to the drug in its pure form.

Different ratios of carriers used also showed different responses. The ratio which showed the best release was considered as the optimized formulation.

Cefixime is semi-synthetic orally active third generation cephalosporin antibiotic. It is currently used for the treatment of respiratory tract infection, otitis media, uncomplicated urinary tract infection and gonorrhea caused by β-lactamase-producing bacteria. However, the low aqueous solubility and poor dissolution of this drug in gastric fluid affects its rate of absorption, resulting in a low and variable oral bioavailability hence a polymeric carrier is added to improve the bioavailability of the drug. Different ratios of solid dispersions were prepared and studied to obtain the best formulation.

Ibuprofen, is a non steroidal anti inflammatory drug (NSAIDs) is widely used as an analgesic and antipyretic, but it has a problem of low solubility in water which leads to potential bioavailability problem. Therefore, enhancement of the aqueous solubility of ibuprofen using a hydrophilic carrier was attempted.

Valsartan is a competitive antagonist of angiotensin II receptor and widely used for the treatment of hypertension. Valsartan has low bioavailability which might be related to its poor aqueous solubility hence a water soluble carrier is combined with it in order to improve the bioavailability and therapeutic efficacy. [1].

Literature Review

S.C. Arora et al. developed and characterized solid dispersion of cefixime trihydrate using solvent evaporation method. The objective of this study was to prepare cefixime trihydrate solid dispersion by solvent evaporation method using urea as a water soluble carrier. The outcome of this study was that, upon preparing the solid dispersion of cefixime, its solubility improved greatly as well as its dissolution studies thus bioavailability improvement was observed [2].

S.Shahid Mohd et al. compared solubility improvement of cefixime and omeperazole magnesium by using solvent evaporation and slugging method. The objective of this study was to improve the solubility of cefixime and omeprazole magnesium by solvent evaporation and fusion methods prepared using urea and PVPK-30 and PEG6000 as carriers . The outcome was that both the drugs prepared with solvent evaporation technique showed higher solubility than before [3].

M. Nafady studied the enhancement of ketoprofen and ibuprofen solubility and dissolution by lyophilized milk (lyophilization method). This work was performed to improve the solubility and dissolution of the poorly water soluble ketoprofen and ibuprofen using lyophilized milk. The result observed after this study revealed that the lyophilized milk used enhanced the solubility by dual effect. This work was performed to improve the solubility and dissolution of the poor water soluble ketoprofen and ibuprofen using lyophilized milk. The result of this work revealed that the used LM enhanced the solubility by dual effect, mixed micelle and incubation of the drug [4].

P.K. Lakshami et al. prepared and comparatively evaluated liquisolid compact and solid dispersion of valsartan. The objective of this study was to improve the solubility of valsartan by preparing its solid dispersion via solvent evaporation method, using nonvolatile solvent and hydrophilic carrier (PG, PEG, and glycerin). This study concluded that solubility of valsartan improved, when prepared using solvent evaporation method, in comparison to traditional solid dispersion of the same drug [5].

Nadia Saffon studied the dissolution profile of ibuprofen solid dispersion prepared with cellulosic polymers and sugar by fusion method. The desired goal of the study was to improve the solubility and dissolution of the NSAID ibuprofen by preparing its solid dispersion form using the fusion method. Solid dispersions of the NSAID, Ibuprofen were prepared and characterized in order to assist in improving its dissolution properties. The researcher studied and evaluated solid dispersions with HPMC and HPC, icing sugar, dextrose, mannitol and lactose. The results collected revealed that solid dispersions prepared by using HPMC and HPC showed improved dissolution rates while on the other hand, the ones which were prepared using icing sugar, dextrose, mannitol or lactose showed drug retarding capability. Moreover, the data obtained from this study lead to a conclusion that higher the concentration of the polymer in the solid dispersion the better dissolution rates it achieves [6].

To improve the bioavailability of ibuprofen, a thorough preformulation trial was undertaken by Ghosh et.al. The probability of improving solubility by solid dispersion technique was also investigated. The in vitro release profiles of the developed tablets showed superiority over the popular marketed tablets [7].

Solid dispersions of ibuprofen (IBF) were prepared by solvent evaporation method using polyethylene glycol 10000 (PEG), talc, and PEG-talc as dispersion carriers by Khan et al. The increase in the IBF dissolution rate from the solid dispersions with the carriers used in this study could be attributed to several factors such as improved wettability, local solubilization, and drug particle size reduction [8].

Ibuprofen-Poloxamer 188 (P 188) binary solid dispersions (SD) with different drug loadings were prepared, characterized by scanning electron microscopy (SEM), differential scanning calorimetry (DSC) and Fourier transform infrared spectroscopy (FTIR), and evaluated for solubility, in vitro release, and oral bioavailability of ibuprofen in rats. Immediate and complete release of ibuprofen from SDs might be because of the reduction in the drug crystalline due to eutectic formation, and their dosing to fasted rats resulted in a significant increase in the area under curve (AUC) of the plasma concentration versus time curve and the maximum plasma concentration (Cmax), and a significant decrease in the time to reach C_{max} (T_{max}) over ibuprofen and physical mixtures [9].

According to Leuner et al. with the advent of combinatorial chemistry and high throughput screening, the number of poorly water soluble compounds has dramatically increased. With the introduction of new manufacturing technologies such as hot melt extrusion, it should be possible to overcome problems in scale-up and for this reason solid solutions are enjoying a renaissance. Leuner et al. an overview of the historical background and definitions of the various systems including eutectic mixtures, solid dispersions and solid solutions [10].

Vasconcelos et al., mentioned that surfactants have been included to stabilize the formulations, thus avoiding drug recrystallization and potentiating the solubility of drugs. New manufacturing processes to obtain solid dispersions have also been developed to reduce the drawbacks of the initial process [11].

Ahuja, N. et al., studied the role of various water-soluble carriers for dissolution enhancement of a poorly soluble model drug, rofecoxib, using solid dispersion approach. Diverse carriers viz. polyethylene glycols (PEG 4000 and 6000), polyglycolized fatty acid ester (Gelucire 44/14), polyvinylpyrollidone K25 (PVP), poloxamers (Lutrol F127 and F68), polyols (mannitol, sorbitol), organic acid (citric acid) and hydrotropes (urea, nicotinamide) were investigated for the purpose. All the solid dispersions showed dissolution improvement vis-à-vis pure drug to varying degrees, with citric acid, PVP and poloxamers as the most promising carriers [12].

Lipinski also studied how poor aqueous solubility can create problems. He explained various techniques including solid dispersion technology [13].

Hypothesis

Formulating the drug with two different parts i.e. hydrophilic and hydrophobic can significantly alter the drug's solubility leading to better drug bioavailability.

Objectives

The main objectives of the present study were as follows:

- To identify and procure poorly soluble drugs available in Oman.
- To evaluate the methods of preparation of solid dispersions.
- To recognize the effective and suitable method of preparation of solid dispersions for different drugs.
- To evaluate the effect of solid dispersion technology on bioavailability of drugs.

Experimental

Materials

Ibuprofen, Valsartan, Hydroxypropylmethylcellulose (HPMC) and Polyvinylpyrolidone (PVP K30) were procured from National Pharmaceutical Industries Co. (SAOG). However, cefixime was obtained from Oman Pharmaceutical Products Co. L.L.C.

Methods

The dispersions were prepared by physical mixture method. Each drug was blended with its suitable carrier in different ratios as described in the table below:

A. Preparation of solid dispersions

Following methods were used for preparing solid dispersions:-

1- Kneading method

In this method, the drug and polymer were mixed with small amount of solvent (methanol) to form thick paste by kneading. The paste then was dried at 45^0C in the oven. The mass was passed through sieve no.22 and the product was packed and kept in a desiccator.

2- Physical mixture

The physical mixtures were prepared by weighing the calculated amount of drugs and carriers and then mixing them in a glass mortar by triturating. The resultant physical mixtures were passed through 44-mesh sieve and stored in desiccators until use for further studies.

The formulae of dispersions are given as below in Table A:

Table A

Drugs	Carriers	Ratios	Concentration of drug (mg)	Concentration of carrier(mg)	Methods used
Cefixime	HPMC	1:1	500mg	500mg	Kneading and physical mixture
		1:2	333mg	666mg	
		1:3	250mg	750mg	
Ibuprofen	PVP K30	1:1	500mg	500mg	Physical mixture
		1:2	333mg	666mg	
		1:3	250mg	750mg	
Valsartan	PVP K 30	1:1	500mg	500mg	Physical mixture
		1:2	333mg	666mg	
		1:3	250mg	750mg	

B. Evaluation of Solid Dispersions of Drugs

Release Studies: The dissolution studies for Valsartan, Ibuprofen and Cefixime, were carried out using the *In-vitro* Dissolution apparatus. It was carried out by adding 100 mg of pure powder of the drug in a 900 ml beaker filled with distilled water. This was surrounded by an adequate hot water bath of 37 °C. Firstly, the apparatus was switched on and the paddle started rotating to distribute the drug inside the 900 ml water beaker. Then, a sample of 5 ml of the solution was withdrawn at zero time and then every 15 minutes for an hour. Each time a sample was withdrawn an equal amount of distilled water was added so that the volume of the solvent was maintained throughout the study for each drug. Finally, results were obtained and collected in the tables presented later in this research.

Preparation of Standard Curve

- First stock solution of each drug was prepared individually by dissolving 100 mg of pure drugs (cefixime, ibuprofen and valsartan) in 100 ml methanol.
- The second stock solution was prepared by taking 10 ml from first stock solution and diluted up to 100 ml.
- Series of dilutions containing 2,4,8,10,12,16,18,20 and 24(mcg/ml) were prepared.
- The absorbance was measured by using UV spectrophotometer. Methanol was used as a blank. Absorbance was plotted against concentrations as shown in Figure 1.

Results

The standard plot is shown in Figure 1.

Table 1 shows the plot of Valsartan absorbance of U.V light vs. different concentrations

Table 1: the plot of Valsartan absorbance of U.V light vs. different concentrations at λ_{max} = 204nm

Concentration (mcg/ml)	Absorbance (λ_{max})
2	0.1962
4	0.2632
8	0.4361
10	0.5118
12	0.5610
16	0.6576
18	0.5895
20	0.6731

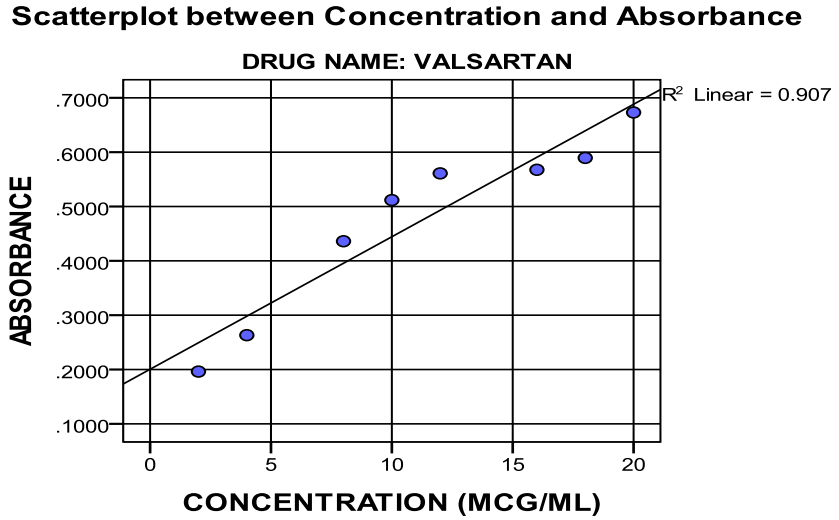

Figure 1: Plot of Concentrations vs Absorbace for pure Valsartan drug

The release studies results were obtained using the in-vitro dissolution apparatus following the procedure described previously in the "Experimental" section and they were as follows:

Dissolution/Release Studies

The results of release studies are as below:-

Dissolution study results for pure 100mg Valsartan drug at different time intervals are shown in Tables V-0 to V-2 as follows:

Table V-0: Pure drug

Time (min)	Absorbance	Concentration (mcg/ml)	Total amount of drug Dissolved (mcg)	% drug released
0	0.0757	5.1790	9322.5	9.3225
15	0.8555	27.3125	49162.5	49.1625
30	0.3355	5.6458	40162.5	40.1625
45	0.2193	0.80417	1447.5	1.4475
60	0.2527	2.1958	3952.5	3.9525

The dissolution study for different Valsartan: carrier ratios was done in the same way that was followed in studying the release of the pure drug and the results for each ratio were collected and tabulated in three tables (V-1 to as shown below:

Table V-1: Dissolution study results for solid dispersions prepared by physical mixture method for Valsartan and carriers mixed in different ratios

Formulation ratio (Drug: carrier)	Time (min)	Absorbance	Concentration (mcg/ml)	Total amount of drug Dissolved (mcg)	% Drug released
1 : 1	15	0.5579	14.9125	26842.5	26.8425
	30	0.7616	23.40	42120	42.12
	45	0.8840	28.5	51300	51.3
	60	0.9286	30.358	54645	54.645

Table V-2

Formulation ratio (Drug: carrier)	Time (min)	Absorbance	Concentration (mcg/ml)	Total amount of drug Dissolved (mcg)	% Drug released
1 : 2	15	0.9993	33.304	59.947.5	59.948
	30	1.2503	43.7625	787725	78.7725
	45	1.4744	53.1	95580	95.58
	60	1.5055	54.39	79912.5	97.9125

Table V-3

Formulation ratio (Drug: carrier)	Time (min)	Absorbance	Concentration (mcg/ml)	Total amount of drug Dissolved (mcg)	% Drug released
1 : 3	15	1.0006	33.358	60045	60.045
	30	1.2887	45.3625	816252	81.6525
	45	1.4737	53.0708	95527.5	95.5275
	60	1.4880	53.667	96600	96.6

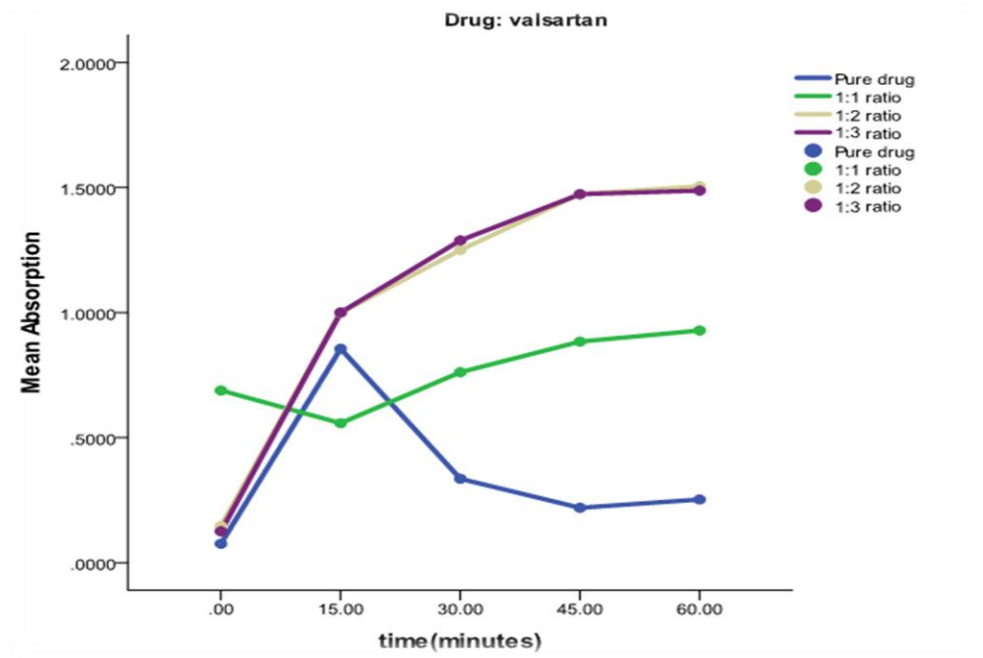

Figure 2: Plot of Absorbance vs time for different ratios of valsartan

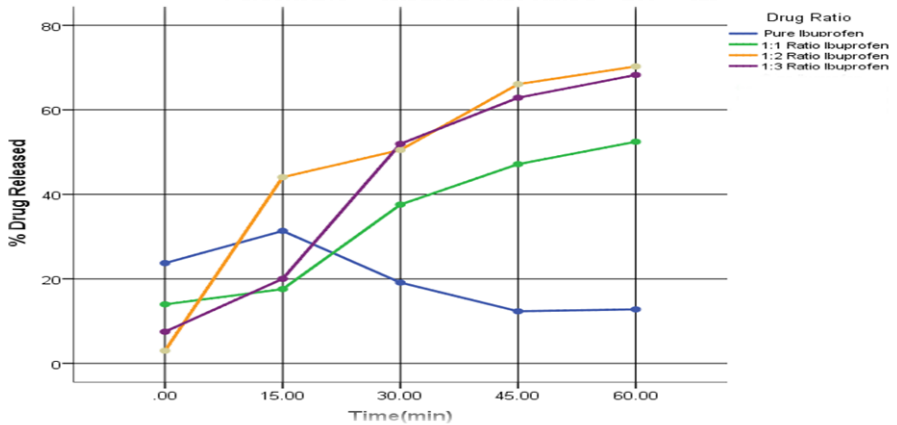

Figure 3: Plot of time vs. % drug released for different Dispersions of Valsartan prepared with various ratios of carrier

Results of Ibuprofen

Table 2 shows Ibuprofen absorbance of U.V light vs. varying concentrations

Table 2

Concentrations (mcg/ml)	Absorbance (λ_{max}) = 224nm
2	0.1306
4	0.280
8	0.2879
10	0.3562
12	0.4912
16	0.5769
18	0.6694
20	0.7460
24	0.8505

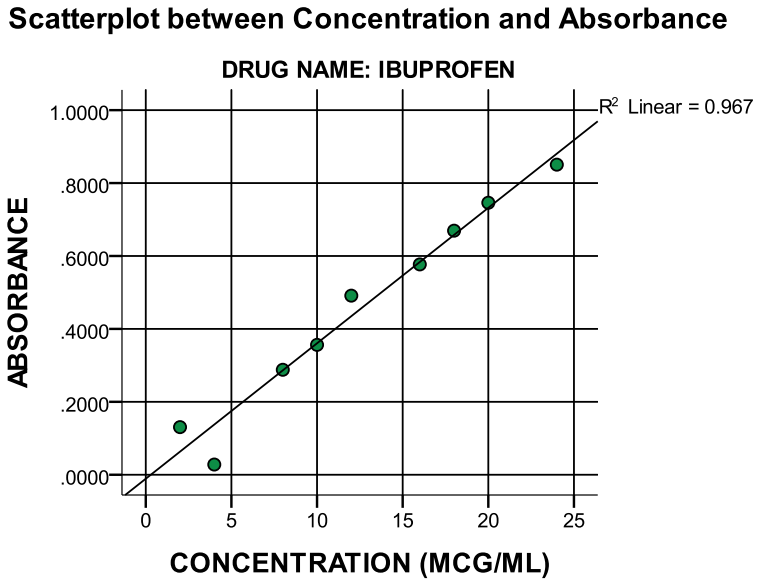

Figure 4: Plot of varying concentrations vs. Absorbance for pure Ibuprofen

Dissolution study results for pure 100mg Ibuprofen in different concentrations are shown in Table I-0 to I- 2

Table I-0

Pure drug (Drug: carrier)	Time (min)	Absorbance	Concentration (mcg/ml)	Total amount of drug Dissolved (mcg)	% drug released
	0	0.4766	13.178	23721.08	23.721
	15	0.6332	17.410	31339.45	31.339
	30	0.3820	10.621	19118.9	19.118
	45	0.2424	6.8486	12327.65	12.327
	60	0.2517	7.10	12780	12.780

Dissolution study results for solid dispersions prepared by physical mixture method for Ibuprofen in different ratios (Table I-1 to I-3)

Table I-1

Formulation ratio (Drug: carrier)	Time (min)	Absorbance	Concentration Mcg/ml	Total amount of drug Dissolved (mcg)	% Drug released
1:1	0	0.2760	7.7656	13960.8	13.9608
	15	0.3501	9.760	17568	17.568
	30	0.7613	20.872	37569.6	37.5696
	45	0.9580	26.190	47142	47.147
	60	1.067	29.135	52443	52.443

Table I-2

Formulation ratio (Drug: carrier)	Time (min)	Absorbance	Concentration (mcg/ml)	Total amount of drug Dissolved (mcg)	% drug released
1:2	0	0.0504	1.6594	2987.02	2.9870
	15	0.8947	24.478	44061.08	44.061
	30	1.02715	28.058	50504.59	50.504
	45	1.3622	37.113	66804.32	66.0804
	60	1.4335	39.040	70272.97	70.272

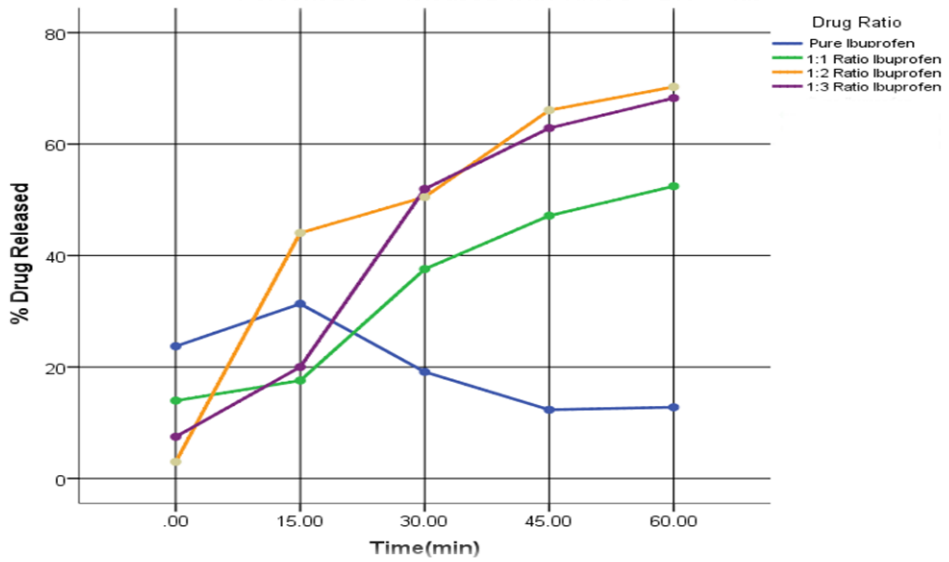

Figure 5: Plot of time vs. % drug released for different Dispersions of Ibuprofen prepared with various ratios of carrier

Table I-3

Formulation ratio (Drug: carrier)	Time (min)	Absorbance	Concentration (mcg/ml)	Total amount of drug Dissolved (mcg)	% Drug released
1:3	0	0.1428	4.1567	7482.16	7.482
	15	0.4003	11.1162	20009.18	20.009
	30	1.0566	28.854	51937.29	51.937
	45	1.2812	34.924	62863.78	62.863
	60	1.3921	37.921	68258.91	68.258

Table 3 shows cefixime absorbance of U.V light vs. varying concentrations

Table 3

Concentration (mcg/ml)	Absorbance (λ_{max}) = 292nm
2	0.0357
4	0.1233
8	0.3213
10	0.4028
12	0.4986
16	0.6735
18	0.7282
20	0.8135
24	0.9817

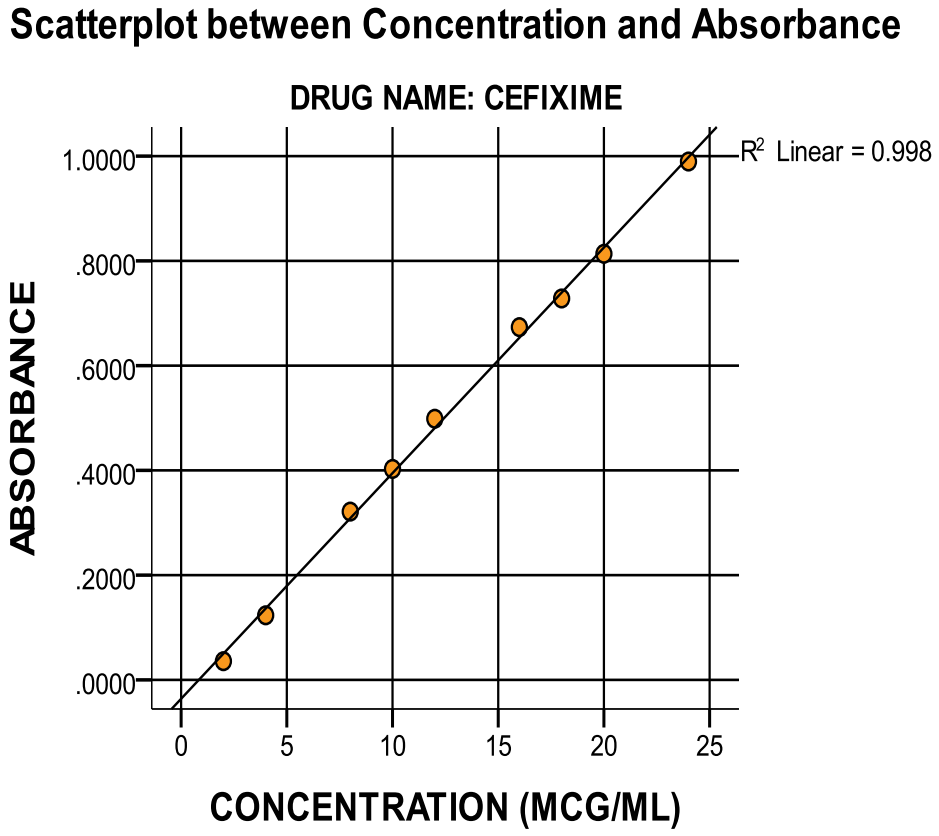

Figure 6: Plot of Concentration vs Absorbance for Cefixime

Dissolution study results for pure 100mg cefixime drug is as shown in Tables C-0 to C-3

Table C-0

Pure drug	Time (min)	Absorbance	Concentration (mcg/ml)	Total amount of drug Dissolved (mcg)	% drug released
	0	**0.0309**	**1.5581**	**2800**	**2.8**
	15	**0.2393**	**6.4023**	**11524**	**11.52**
	30	**0.5810**	**14.348**	**25827**	**25.8**
	45	**0.3251**	**8.397**	**15115**	**15.1**
	60	**0.2814**	**7.381**	**13286**	**13.2**

Dissolution study results of solid dispersions prepared by physical mixture method for cefixime and carriers in different ratios

Table C-1

Formulation ratio	Time (min)	Absorbance	Concentration (mcg/ml)	Total amount of drug Dissolved (mcg)	% Drug released
1:1	0	0.0054	0.9627	1733	1.7
	15	0.1724	4.8465	8723	8.7
	30	0.3842	9.772	17584	17.5
	45	0.5905	14.569	26224	26.2
	60	0.7147	17.458	31424	31.4

Table C-2

Formulation ratio	Time (min)	Absorbance	Concentration (mcg/ml)	Total amount of drug Dissolved (mcg)	% drug released
1:2	0	0.2140	5.8139	10465	10.4
	15	0.5466	13.548	24387	24.3
	30	0.6224	15.311	27560	27.5
	45	0.6804	16.660	29988	29.9
	60	0.7988	19.4139	34945	34.9

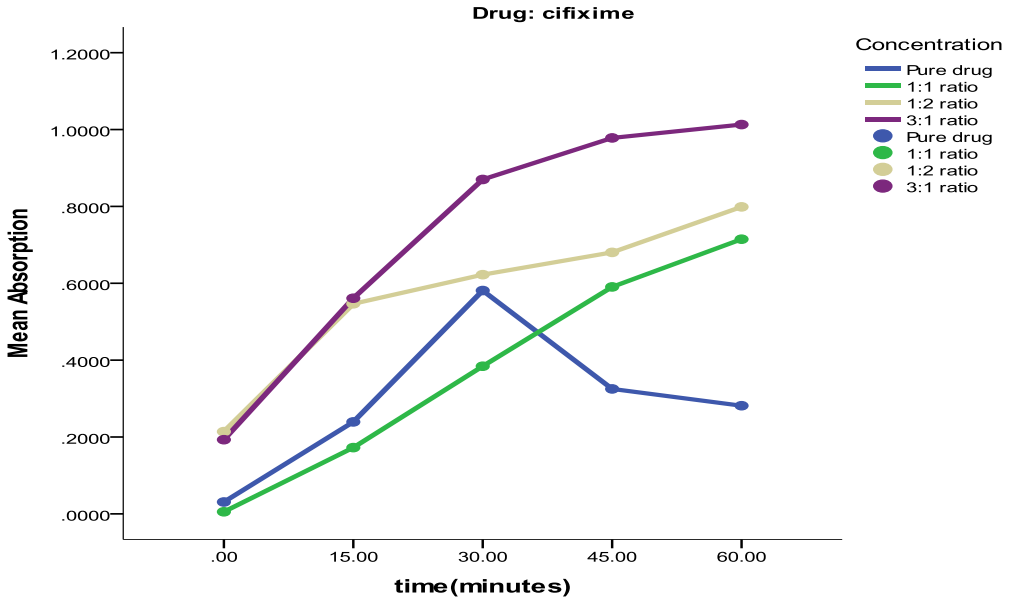

Figure 6: Plot of time VS absorbance for different dispersions of Cefixime

Table C-3

Formulation ratio	Time (min)	Absorbance	Concentration (mcg/ml)	Total amount of drug Dissolved (mcg)	% drug released
1:3	0	0.1930	5.3255	9586	9.5
	15	0.5611	13.886	24994	24.9
	30	0.8701	21.072	37929	37.9
	45	0.9782	23.586	42454	42.4
	60	1.0130	24.395	43911	43.9

Discussion

Solid dispersions of Valsartan using different ratios of carrier (Polyvinylpyrrolidone (PVP K-30)) were formulated by physical mixture method and observed for the *in-vitro* release by using Rotary Paddle/Basket apparatus.

Sample analysis was done using U.V spectrophotometer at 240nm. The dissolution profile was studied by plotting percent drug released versus time.

Similarly, dissolution studies were performed for pure drug and for its solid dispersion using different carrier: drug ratios.

As the dissolution graph for Valsartan presented above shows, there is a noted difference between the solubility/dissolution of the drug and the solid dispersion of it in 1:2 and 1:3 ratios as they showed almost similar solubility and was better in comparison to the 1:1 ratio.

Solid dispersions of ibuprofen using different ratios of carrier (Polyvinylpyrrolidone (PVP K-30)) were formulated by physical mixture method and observed for the *in-vitro* dissolution by using Rotary Paddle/Basket apparatus.

Sample analysis was done using U.V spectrophotometer at 224 nm. The dissolution profile was studied by plotting percent drug released versus time.

Similarly, dissolution studies were performed for pure drug and for its solid dispersion with different carriers in different ratios.

The percentage of the drug released increased from 12.78 to 52.4% (1:1 ratio), 70.2% (1:2 ratio) and 68.2% (1:3 ratio). Thus solid dispersion of ibuprofen in 1:2 ratio was considered the best formulation as it increased the solubility of ibuprofen from 12.8 to 70.2 %.

The use of cefixime with hydroxypropymethylcellulose (HPMC) greatly improved the solubility of the drug and enhanced its dissolution rate.

Sample analysis was done using U.V spectrophotometer at 292 nm. The dissolution profile was studied by plotting percent drug released versus time.

Similarly, dissolution studies were performed for pure drug and for its solid dispersion using different carrier: drug ratios.

The percentage of the drug released increased from 13.2 to 31.4% (1:1 rstio), 34.9% (1:2 ratio) and 43.9% (1:3 ratio), thus solid dispersion of cefixime in 1:3 ratio was considered as the best formulation as it increased the solubility of cefixime from 13.2 to 43.9%.

Conclusion

The objective of the study was achieved by improving the solubility of the poorly soluble drugs namely Valsartan, Ibuprofen and Cefixime. The key factor for such an improvement was mixing the drugs with the suitable carriers such as Hydroxypropylmethylcellulose (HPMC) and polyvinylpyrrolidone (PVP K30) in different ratios to obtain the best solid dispersion formulation for each drug. The results obtained were compared and the best formulation for each of the drugs was revealed as discussed in the discussion part for each drug.

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