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OPTIMIZATION OF ETHYL CELLULOSE CONCENTRATION IN EXTENDED RELEASE FORMULATION OF HYPOGLYCEMIC AGENT

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ABSTRACT

The aim of the present investigation was to optimize the effect of ethyl cellulose (EC) concentration in extended release solid dispersion formulations of Glibenclamide (GLB) with using polyvinyl pyrrolidone (PVP) as a hydrophilic release retardant polymer. Glibenclamide is a oral hypoglycemic agent having short biological half-life of 3-4 hrs and therefore extended release medication is required to get prolonged effect. A 2^3 full factorial design were used for formulation composition and all formulations were developed using solvent evaporation method. The in vitro release studies were performed using US Pharmacopoeia type II apparatus (paddle method) in 900 ml of pH 7.4 phosphate buffer at 100 rpm. The release profiles were analyzed using statistical method (one-way analysis of variance) and similarity factor (f2) values. The results in the present investigation confirm that the release rate of the drug with PVP solid dispersion is highly influenced by the drug/EC ratio. The formulation F2 containing EC and PVP (1:1) was found to be promising. Formulation F2 showed maximum drug release in 8 hrs along with satisfactory extended release mechanism. The developed extended release formulation of Glibenclamide may be used in clinic for prolonged drug release in stomach for at least 8 hrs, thereby improving the bioavailability and patient compliance.

Keywords: Glibenclamide, Ethyl cellulose. Polyvinyl pyrolidone, Solid dispersion formulation.

INTRODUCTION

An ideal drug delivery system should be able to deliver an adequate amount of drug for an extended period of time for its optimum therapeutic activity. Most drugs are inherently not long lasting in the body and require multiple daily dosing to achieve the desired blood concentration to produce therapeutic activity. To overcome such problems greater attention has been focused on sustained release drug delivery system. Conventional dosage form a as to be administered several times to produce therapeutic efficacy, which yields fluctuations in plasma level. Repetitive dosing of drug causes poor compliance among the patients. Sustained release formulations can be utilized to avoid repetitive dosing of drugs in a day. Diabetes is one of the major causes of death and disability in the world. The latest, WHO estimate for the number of people with diabetes worldwide, in 2000, is 171 million, which is likely to be at least 366 million by 2030. The focus of medical community is on the prevention and treatment of the disease, as is evident from the rising number of research papers every year on the subject. The term solid dispersions was initially used by Sekiguchi and Obi and applied to systems in which the drugs are homogeneously dispersed within a carrier. The methodology to make solid dispersions includes co-fusion, co-dissolution in a proper solvent or a mix of both ((Aceves et al 2000). Solid dispersion techniques are widely applied to increase the apparent solubility or enhance the oral bioavailability of poorly water-soluble compounds. However, despite many papers, which suggested that the release mechanisms of drugs from a variety of solid dispersions depend on the physical properties of carriers as well as drug substances, preparation methods and so on, basic principles of their dissolution mechanism have not been understand sufficiently (Ohara et al 2005).

MATERIALS AND METHODS

Materials

Glibenclamide was a gift sample from Akums Pharmaceutical Ltd, Haridwar. Polyvinyl pyrrolidone (PVP) and Ethylcellulose (EC) was purchased from Loba Chemie Pvt. Ltd., Mumbai India. All other chemicals and solvents were of analytical grade.

Methods

Drug Excipient Compatibility Studies

To study the Glibenclamide compatibility with different formulation excipients Fourier transform infrared spectroscopy (FTIR) and Differential scanning calorimetry (DSC) were done. FTIR, DSC studies are performed on samples of GLB pure drug, solid dispersion of GLB with different polymers in different drug to polymer ratio. The IR Spectra of the test samples were obtained using ATR method and the spectra were obtained between the wave number range of 4000-400cm-1.DSC studies were performed using a DSC (diamod, Mettler star) with thermal analysis data system, computer, and a plotter interface. Indium/zinc standards were used to calibrate the temperature and enthalpy scale. Accurately weighed 5-6 mg samples were hermetically sealed in aluminum pans and heated at constant rate of 10oC/min over a temperature range of 40 ^{o}C to 300^{o}C and inert atmosphere was maintained by purging nitrogen gas at a flow rate of 50ml/min.

pH Partition Study

The partition co-efficient of the drugs was determined using n-octanol: water system. The n-octanol- water partition coefficient serves as a parameter of lipophilicity. In order to perform this study, Octanol and water were mixed in the ratio of 50:50, and were shaked for 30 minutes in a separating funnel. Aqueous phase was discarded. Now 10 ml of organic solution was mixed with 10 ml of 1.2 pH gastric simulated HCl buffer solution containing 10 mg of drug and shaken it for 5 minutes. Now organic phase was discarded and absorbance of aqueous phase was observed at 300 nm. Same procedure was repeated with phosphate buffer (pH 6.8 & 7.4 pH) and borate buffer pH 9.5.

Preparation of solid dispersion

A full 2^3 factorial design were used for preparation of solid dispersion. The extended release solid dispersions of Glibenclamide were prepared by physical methods and solvent evaporation method, using various concentrations of ethyl cellulose (EC) and polyvinyl pyrrolidone (PVP) (Table 1-3).

Factor A: concentration of EC

Factor B: concentration of PVP

Table: 1 Actual and coded values of factors

Factor	Actual values(mg)			Coded values		
	Low	Mid	High	Low	Mid	High
Factor A (EC)	50	100	150	-1	0	+1
Factor B (PVP)	100	300	500	-1	0	+1

Table: 2 Composition of the formulation in terms of coded values for EC Concentration optimization

Formulation	EC	PVP
F1	+1	+1
F2	0	0
F3	-1	-1
F4	+1	-1
F5	-1	+1
F6	+1	0
F7	0	+1
F8	0	-1
F9	-1	0

Table: 3 Composition of formulations for EC Concentration optimization

Formulation	Drug (mg)	EC (mg)	PVP (mg)
F1	100	150	500
F2	100	100	300
F3	100	50	100
F4	100	150	100
F5	100	50	300
F6	100	150	500
F7	100	100	500
F8	100	100	100
F9	100	50	300

Physical mixture

Physical mixtures were prepared by mixing the powered drug and polymers in a mortar. Glibenclamide and two different polymers in different drug to polymer ratios were accurately weighed, mixed for 15 minutes than sifted through sieve no. 44 and stored in desiccators under vacuum until use.

Co-evaporation method

GLB and different carriers were taken in different drug to ratios EC: PVP mixed well and dissolved in minimum quantities (10 ml) of chloroform and stirred for 2 to 4 hours until clear

solution was obtained. The solvent was evaporated at 40°C in a water bath and then dried completely in vacuum desiccators for two days. The solid sample was ground gently with a mortar pestle and passed through a 44 mesh sieve.

Drug content studies

PMs and SDs equivalent to 10 mg of GLB were accurately dissolved in minimum amount of selecting a solvent dimethylsulfoxide (DMSO) in which polymers was insoluble but drug was soluble. The drug content was determined at spectrophotometrically at 300.0 nm using calibration curve based on standard solutions in phosphate buffer (pH 7.4)

Determination of *in vitro* drug release of solid dispersions:

In vitro dissolution was performed using USP XXXVII Apparatus II in 900 ml of phosphate buffer (pH 7.4) at an agitation rate of 100 rpm. The temperature of the medium was maintained at 37°C±1°C. 10 mg of drug or its equivalent weight of the prepared dispersions were taken and analyzed for dissolution. A 5.0 ml sample was withdrawn at specific time points over a 10 hour period and equal volume of fresh dissolution medium was added to maintain a constant volume. The aliquots were filtered and the drug concentration was determined by spectrophotometry.

RESULTS AND DISCUSSION

Drug Excipient Compatibility Studies

Drug was mixed with excipients in different ratio. These mixtures were kept in a 5 ml glass vial and kept for 30 days at 40^0C/75%RH .At the end of 30 days all formulations were physically and chemically analyzed. During physical interaction it was found that none of the samples shown organoleptic property like discoloration, caking, liquefaction and gas formation. It indicates that drug and excipients are compatible with each other. It can be concluded that there was no physical incompatibility of glibenclamide with the excipients.(Table No. 4)

Table 4 Drug excipients physical compatibility study

S.No.	Mixture	Liquefaction	Caking	Discoloration	Odour or gas formation
1	GLB	NC	NC	NC	NC
2	GLB+EC	NC	NC	NC	NC
3	GLB+PVP	NC	NC	NC	NC
4	GLB+EC+PVP	NC	NC	NC	NC

***NC indicates NO CHANGE**

The FT-IR graphs of drug alone and also of drug with both polymers were taken. There were not appeared any extra peaks found in all cases so finally it was concluded that the excipients were compatible with drug.

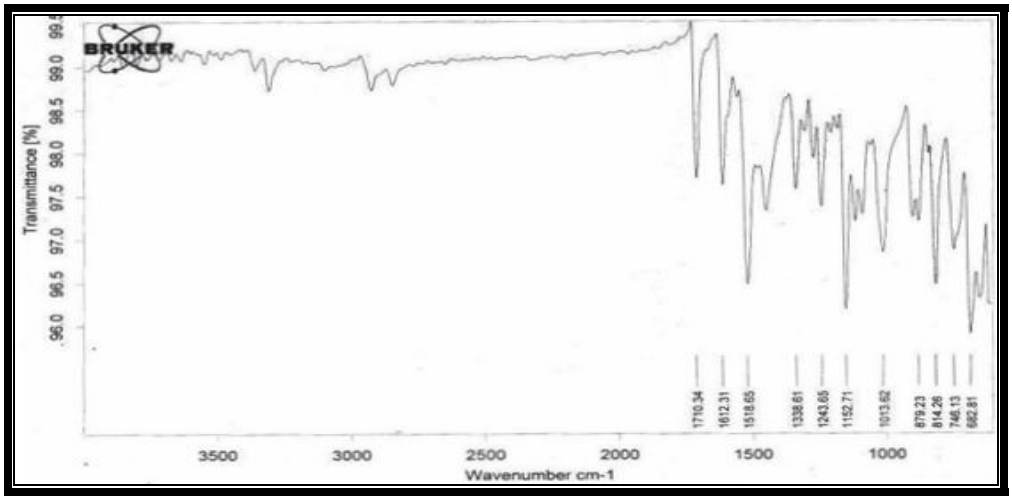

Figure 1: IR spectra of Glibenclamide

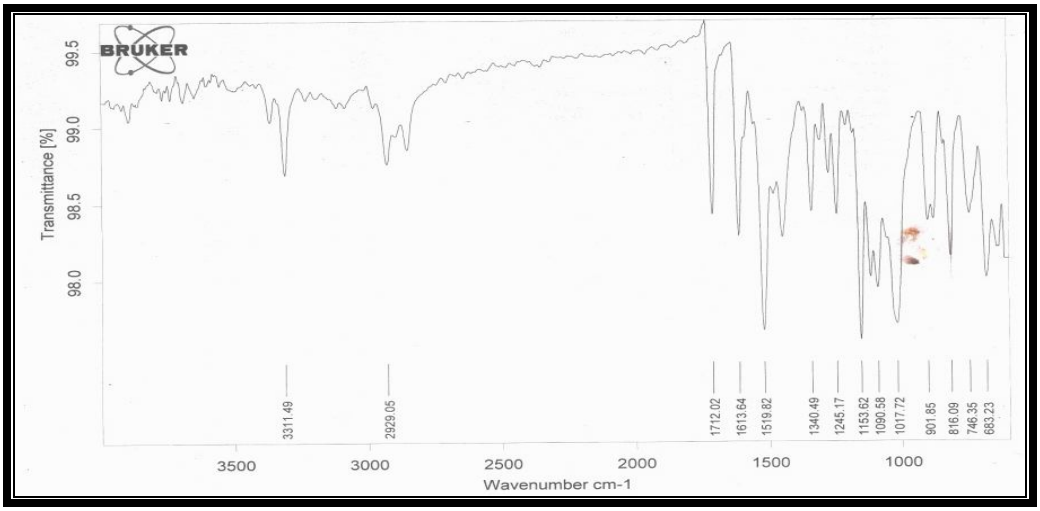

Figure 2: IR spectra of GLB + EC + PVP

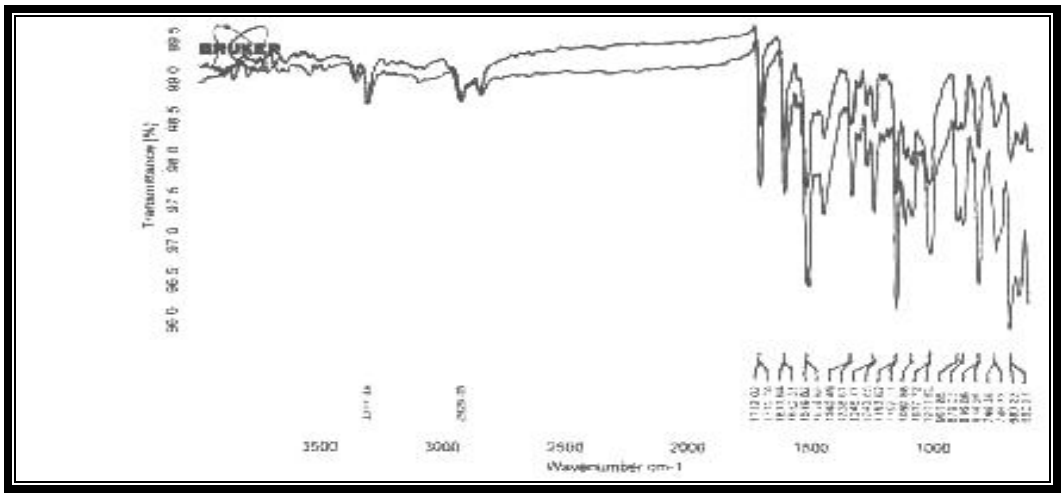

Figure 3: Overlay IR spectra of GLB + EC + PVP with GLB

DSC runs for SDs indicated significant suppression of the drug endothermic peak, suggesting a homogeneous dissolution of the drug in polymers. The thermograms of SDs showed an endothermic peak of the corresponding EC and PVP carriers along with a very shallow endotherm at around 170°C of GLB, indicating presence of residual crystallinity of GLB, where as SDs did not show any melting endotherm of GLB. It might be due to the presence of less crystalline form of GLB in the SDs or the dissolution of crystalline GLB into the moltan carriers. In the GLB/PVP systems, precedent melting of PVP promoted the mobility of PVP molecules and its probability of interaction with GLB was increased. The interaction further progressed during the heating process. It may be concluded that, there is no much difference in the melting point of the drug in the thermographs of drug and that of in the formulation so, indicate that the drug is in the same pure state even in the formulation without interacting with the polymers.

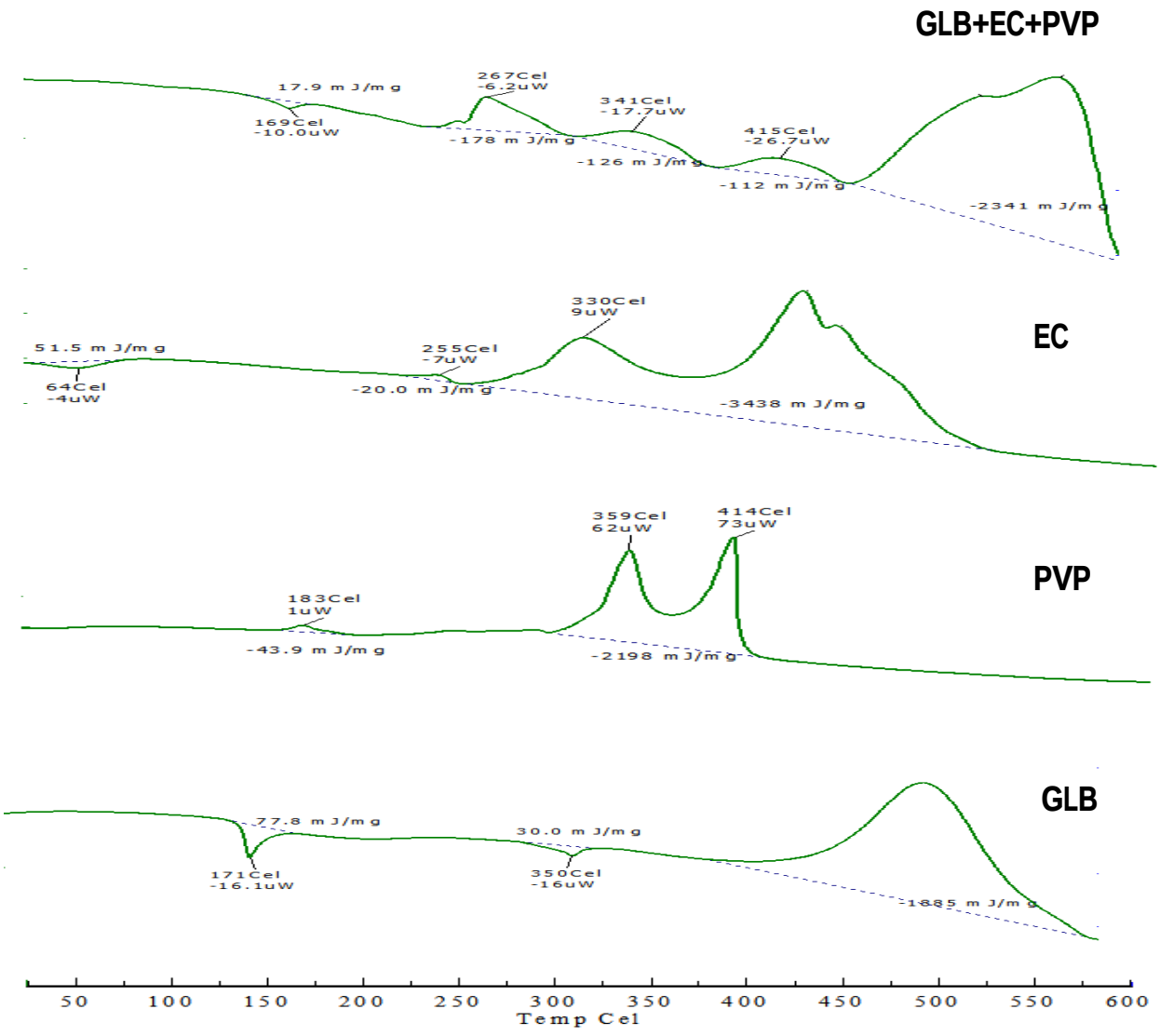

Figure 4: DSC Thermograms of GLB, PVP, EC and Mixture of GLB+EC+PVP

From the above Drug – Excipient compatibility studies data, it is clear indicated that the Glibenclamide was compatible with all the excipients in all ratio tested above. Moreover, these excipients can be used in a marketed formulation of Glibenclamide, has a long shelf life.

pH Partition Study

The pH partition behavior of GLB was estimated and observed that the P value of drug in gastric HCl buffer pH 1.2 was found maximum and in borate buffer pH 9.5 was minimum. Since GLB is an acidic compound whose ionic dissociation state is changeable with pH, hydrophobicity of GLB may change with pH, especially near the pH of its p*K*a (5.3). From the above study it can be concluded drug was undissociated with increasing ph, indicating available for absorption from all g.i.t. sites. Drug Solubility at different pH of buffer solution (gastric HCl buffer pH 1.2, phosphate buffer 6.8 pH, phosphate buffer 7.4 pH and borate buffer pH 9.5) in aqueous phase and organic phase is represented through bar graph. (Figure and Table No. 5)

Table 5: pH partition behavior of GLB in different pH of buffer solution

S. No	Medium	Aqueous Phase (mg/ml)	Organic Phase (mg/ml)
1	Gastric HCl buffer pH 1.2	0.126±0.05	9.874±0.005
2	Acetate buffer pH 4.5	0.93±0.0007	9.079±0.006
3	Phosphate buffer 6.8 pH	1.189±0.0001	8.811±.0004
4	Phosphate buffer 7.4 pH	4.74±0.008	5.269±.003
5.	Borate buffer pH 9.5	7.78±0.0005	2.225±0.006

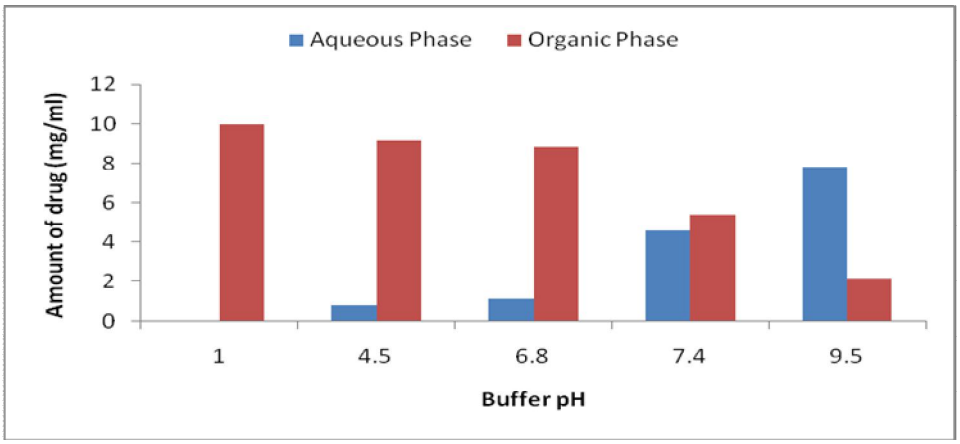

Figure 5: pH partition study of drug at different pH

Optimization of ethyl cellulose concentration

Ethyl cellulose was optimized by evaluating drug content and *in –vitro* release kinetics study. The all batches were subjected for evaluation of the drug content (Table no.6) and in vitro dissolution studies in phosphate buffer pH 7.4. (Table no.7) The drug content of all the formulation was found to be within limit all formulation had the drug content from 91.66±0.40 to 100.00 ±0.7001 % (Figure No.6) and it was found that all the batches performance release of drug very from 5 to 10 hours. However, among all nine batches, the batch no. F2, F7 and F8 are showing good retard release of drug. F2 and F7 the drug above 80% -90% within 8 hrs. and one of them batch no. F2 retard released of drug 99 % within 10 hours, (Figure No. 7 and 8) which is one of the best release performance among all nine batches, whereas F4 and F6 formulation retard the release about 66% within 10 hrs that may be suitable for controlled release.

During in vitro dissolution study, It was observed that release of drug was affected by concentration of EC. When concentration of EC was used below 1%, the drug release was not retard considerably indicating drug molcule not effectively adsorbed on EC surface and when concentration of EC was used above 1%, the drug release was strongly retard upto 1 hours and release only 40% - 50% during first 5 hrs, indicating stronger adsorbetion of GLB on EC surface but when EC was used 1% concentration the drug release was reatard for 8 hours to 10 hours, So therefore 1% concentration of EC concentration was used for formulation of solid dispersion prepared by suspending method and dissolving method.

Table 6: Drug content profile of solid dispersion prepared by solvent evaporation method.

S. No.	Formulations	Loading efficiency (mg)		Percent incorporation
		Theoretical drug content (wt. of solid dispersion)	Actual drug* content	
1	F1	10 (75)	9.61	96.11± 0.4041
2	F2	10 (50)	9.69	96.94± 0.4359
3	F3	10 (25)	9.22	92.22± 0.3047
4	F4	10 (35)	9.44	94.44± 0.4041
5	F5	10 (65)	10.00	100.00±0.7001
6	F6	10 (55)	9.75	97.50± 0.7000
7	F7	10 (70)	9.94	99.44± 0.7002
8	F8	10 (30)	9.81	98.15± 0.4041
9	F9	10 (45)	9.16	91.66± 0.4099

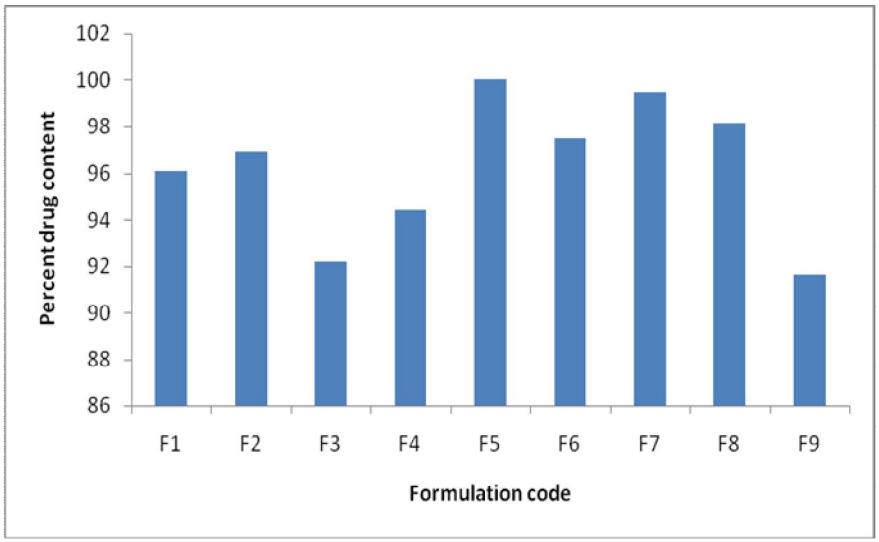

Figure 6: Comparative Drug content profile of formulation F1-F9 in phosphate buffer pH 7.4

Table 7: Cumulative %drug release of formulations F1-F9 in Phosphate buffer pH 7.4

Time (Hrs)	Cumulative % drug release ± S.D. in phosphate buffer pH 7.4								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	5.19± 0.174	12.89± 0.182	17.89± 0.235	7.40± 0.414	19.49± 0.414	8.21± 0.007	2.98± 0.031	15.80± 0.52	16.92± 0.515
2	10.30± 0.258	28.89± 0.124	56.39± 0.414	13.24± 0.717	43.99± 0.616	17.43± 0.001	12.57± 0.051	29.05± 0.61	35.37± 0.212
3	17.68± 0.222	46.43± 0.497	90.02± 0.365	27.54± 0.212	71.42± 0.215	25.53± 0.002	25.05± 0.414	45.87± 0.717	78.75± 0.313
4	27.57± 0.139	53.66± 0.492	94.36± 0.219	33.89± 0.345	96.99± 0.851	33.23± 0.008	29.67± 0.715	58.61± 0.414	96.50± 0.007
5	33.71± 0.203	65.84± 0.429	98.15± 0.213	41.31± 0.414	99.99± 0.313	43.08± 0.007	35.71± 0.065	72.78± 0.212	99.90± 0.021
6	46.82± 0.179	78.94± 0.369		48.19± 0.717		45.53± 0.009	57.84± 0.061	89.70± 0.313	
7	53.01± 0.308	89.78± 0.189		56.14± 0.325		56.92± 0.007	74.42± 0.095	92.25± 0.145	
8	59.83± 0.346	94.42± 0.250		59.32± 0.616		58.97± 0.002	88.93± 0.047	99.89± 0.315	
9	56.19± 0.421	98.03± 0.393		61.44± 0.414		62.05± 0.006	97.58± 0.061		
10	55.15± 0.336	99.07± 0.202		63.02± 0.045		64.00± 0.006	99.59± 0.058		

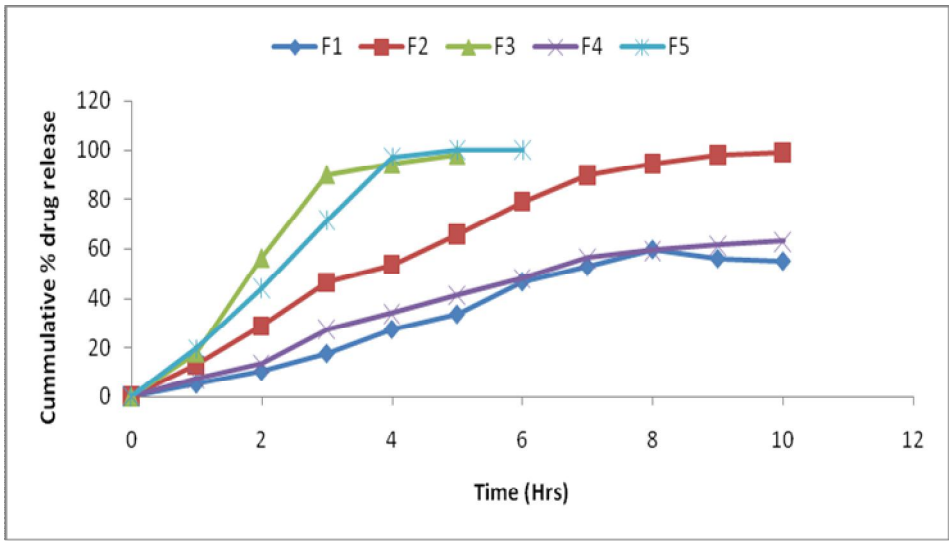

Figure 8: Comparative % drug release of formulations F1-F5 in phosphate buffer pH 7.4

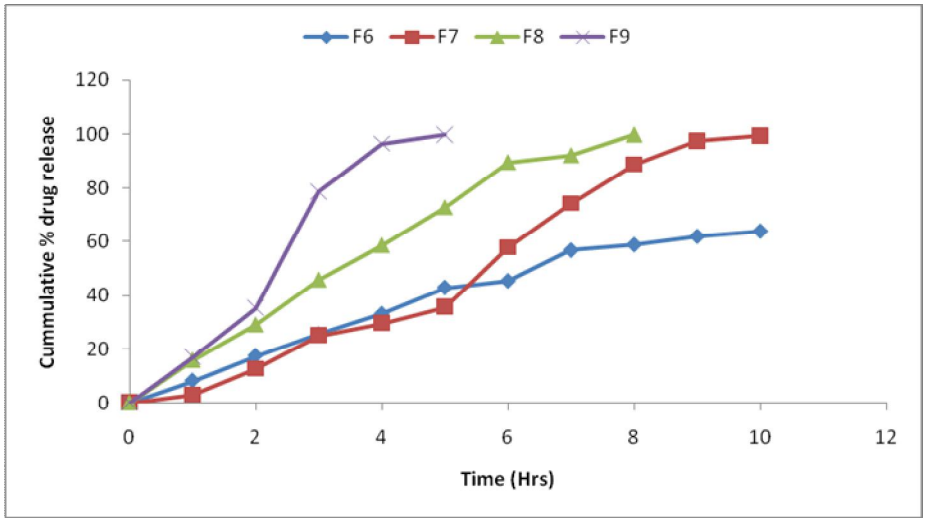

Figure 4.19: Comparative % drug release of formulations F6-F9 in phosphate buffer pH 7.4

CONCLUSION

SDs of poorly water-soluble drug (GLB) were successfully prepared by dissolving technique using ethyl cellulose with the aid of PVP as a hydrophilic matrix. DRIFT spectroscopy revealed possibility of H-bonding interactions in both PMs and SDs. SDs exhibited dramatical improvement in initial rate as well as extent of in vitro drug dissolution. Thus, present study demonstrates the high potential of dissolving techniques for obtaining SDs of poorly water-soluble drugs using with desired release profile. The studies provided better

forecasting and understanding of particulate systems to be incorporated to develop delivery systems.

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