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Studies to Improve Dissolution Properties of Poorly Soluble Carbamazipine by Solid Dispersion

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Abstract

The objective of the study was to improve the aqueous solubility and dissolution of carbamazepine, a poorly water soluble anti-epileptic drug by solid dispersion technique, using water soluble polymers. Solid dispersion of drugs was prepared by physical mixing, fusion and solvent evaporation method. The drug along with the polymers was heated first and then hardened by cooling to room temperatures. They were then pulverized, sieved, and then drug release was studied by the USP basket method at 75 rpm and 37±0.5°C. In this experiment sodium lauryl sulfate (SLS), acetone, hydroxy propyl cellulose (HPC), polyethylene glycol (PEG) 6000, PEG 4000, poloxamer 407, hydrory propyl methyl cellulose (HPMC) 6cps, HPMC 15cps, Polyvinyl pyrrolidine (PVP) K30, PVP K12, and glyceryl monostearete (GMS) were used as polymers. Distilled water was used as dissolution medium. The amount of drug was measured from the absorbance of UV spectrophotometer at 288 nm. The release of drug was plotted in zero order, 1st order, Hixson Crowel and Higuchi release pattern. The study shows that all the polymers enhanced the release profile of carbamazepine. The polymers are thought to serve as dispersing or emulsifying agents for the liberated drug, thus preventing the formation of any water-insoluble surface layers. The correlation coefficients values of the trend lines of the graphs showed that the formulations best fit in Higuchian release pattern.

Key words: Solid dispersion, carbamazepine, dissolution, bioavailability.

Introduction

Carbamazepine, a dibenzapine derivative with structure resembling the tricyclic antidepressans, is used to control some types of seizures in the treatment of epilepsy. It is also used to relieve pain due to trigeminal neuralgia. One of the major problems with this drug is its very low solubility in biological fluids and its biological half-life between 18 to 65 h that results into poor bioavailability after oral administration (Reynolds, 1993; McNaman *et al.*, 1996). It shows erratic dissolution profile in gastric and intestinal fluid due to its poor water solubility. Rate of absorption and/or extent of bioavailability for such insoluble drug are controlled by rate of dissolution in gastrointestinal fluids. The conventional carbamazepine tablets yield peak plasma concentration varying from 4 to 32 h. Stable carbamazepine concentrations occur usually within 2–3 weeks after initiation of therapy (Bauer and Larry, 2008). The effort to improve the dissolution and solubility of a poorly water-soluble drug remains one of the most challenging tasks in drug development. Several methods have been introduced to overcome this problem like solid dispersions, complexation, Zydis technology, and by the use of hydrophilic carriers (Loganathan *et al*., 2000).

Solid dispersion, which was introduced in the early 1970s (Chiou and Riegelman, 1971), is essentially a multi-component system, having drug dispersed in and around hydrophilic carrier(s). Solid dispersion technique has been used for a wide variety of poorly aqueous soluble drugs such as nimesulide, ketoprofen, tenoxicam, nifedipine, nimodipine, ursodeoxycholic acid and albendazole. Various hydrophilic carriers, such as polyethylene glycols, polyvinylpyrrolidone, hydroxypropylmethylcellulose, gums, sugar, mannitol and urea have been investigated for improvement of dissolution characteristics and bioavailability of poorly aqueous-soluble drugs. Solid dispersion can be prepared by various methods such as solvent evaporation and melting method. Solid dispersion technique has been extensively used to increase the solubility of a poorly water-soluble drug. In this technique, a drug is thoroughly dispersed in a water-soluble carrier by suitable method of preparation. The mechanism by which the solubility and the dissolution rate of the drug is increased includes: firstly, the particle size

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of a drug is reduced to submicron size or to molecular size in the case where solid solution is obtained. The particle size reduction generally increases the rate of dissolution; secondly, the drug is changed from crystalline to amorphous form, the high energetic state which is highly soluble; finally, the wettability of the drug particle is improved by the dissolved carrier (Serajuddin, 1999; Leuner and Dressman, 2000). In the present investigation, solvent evaporation method was employed for the preparation of carbamazepine solid dispersions. The carriers used were polyvinyl pyrrolidone (PVP) K-30, polyethylene glycol (PEG) 4000 and PEG 6000. The samples were prepared at various drug-to-carrier weight ratios (Hirasawa *et al*., 2009).

Drug substances are seldom administered alone, but rather as part of a formulation in combination with one or more non-medicinal agents that serve varied and specialized pharmaceutical function. The proper design and formulation of a dosage form requires consideration of the physical, chemical and biological characteristics of all the drug substances and pharmaceutical ingredients to be used in fabricating the product. An important physical-chemical property of a drug substance is solubility, especially aqueous system solubility. A drug must possess some aqueous solubility for therapeutic efficacy. However 35-40 % of the new drugs suffer from poor aqueous solubility. The solubility/dissolution behavior of a drug is key determinant to its oral bioavailability, the latest frequency being the rate-limiting step to absorption of drugs from the gastrointestinal tract. Consequently poor solubility results in low bioavailability, increase in the dose, large inter- and intra-subject variation and large variations in blood drug concentrations under fed versus fasted conditions (Babu *et al.*, 2003; Senthilkumar and Sirisha, 2011).

Thus the rationality of the ongoing study lies in meeting the challenge to improve the dissolution rate as well as bioavailability of poorly water soluble carbamazepine through solid dispersion technique. Several attempts using water-soluble carriers have been made to prepare different formulations of carbamazepine solid dosage forms with improved dissolution properties (Vippagunta *et al*., 2002).

Materials and Methods

Drugs and chemicals: Carbamazepine (Xamim, China), acetone (MERCK, Germany), distilled water (University Laboratory), HPMC 6cps (Samsung, Korea), HPMC 15 cps (MERCK, Germany), HPC (Samsung, Korea), PVP K30 (MERCK, Germany), PVP K12 (MERCK, Germany), poloxamer 407 (BASF), glyceryl monostearate (Samsung, Korea), sodium lauryl sulphate (MERCK, Germany), lactose (Mingel, Germany), paraffin liquid (MERCK, India) etc.

Preparation of solid dispersion by physical mixing method: The active drug was taken into vials. Then the excipients were measured accurately and added into each vial according to Table 1. The physical mixing was carried out by means of shaking the vials slowly and then the mixture was poured in the wax paper and mixed by the help of a spatula.

Table 1. Formulation of carbamazepine solid dispersion by physical mixing method.

Item	Formulation code (amount in mg)			
	F1	F2	F3	F4
Carbamazepine	100	100	100	100
Poloxomer	100	100	100	100
PVP K12	100			
PVP K30		100		
PEG 6000			100	
GMS				100

Finally, the mixture was passed through 40 mesh sieve and lactose was added on each mixture. After mixing well the formulations were kept in desiccators until the dissolution started.

Preparation of solid dispersion by fusion method: The active drug, carbamazipine, was accurately weighed and taken in glass vials. Then 100 mg of each polymer were weighed accurately and taken in it each according to Table 2. After that each of the vials was heated on a water bath containing paraffin liquid to melt the ingredients at a temperature of 120^{o}C. Then drug and polymer combination was cooled with constant stirring to disperse the drug throughout the mixture homogeneously. Finally the formulations were withdrawn from vials, crushed in mortar and pestle, passed through 40 mesh sieves. The

Table 2. Formulation of carbamazepine solid dispersion by fusion method.

Item	Formulation code (amount in mg)								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Carbamazepine	100	100	100	100	100	100	100	100	100
Poloxomer 407	100	100	100	100	100	100	100	100	100
PVP K12	100								
PVP K30		100							
HPMC 6cps			100						
HPMC15cps				100					
Sodium lauryl sulfate					100				
PEG 4000						100			
PEG 6000							100		
GMS								100	
HPC									100

resulted samples were weighed and transferred to fresh vials with proper labeling and its double amount of lactose was added on each vials. After mixing well the formulations were kept in desiccators until the dissolution started.

Preparation of solid dispersion by solvent evaporation method: At first carbamazipine was weighed accurately and taken into dry and clean glass vials. 5 ml acetone was added on each vial. Then each polymer was dissolved in the solvent using a vortex mixer to make a polymer solution according to Table 2. Drug, polymer and solvent combination was dried by using hair dryer until solid dispersion was formed. The formulations were withdrawn from vials, crushed in mortar and pestle, passed through 40 mesh sieves. Then the resulted samples were weighed and transferred in fresh vials with proper labeling and its double amount of lactose was added on each vials and mixed well. Formulations were kept in desiccators until the dissolution started.

In vitro dissolution study of carbamazepine from solid dispersion: In vitro dissolution study was performed in a paddle type dissolution apparatus (USP Type). In case of fusion and solvent evaporation methods, a fixed amount of solid dispersion formulation containing 20 mg equivalent of carbamazepine from each batch and 50 mg equivalent of carbamazepine for physical mixing method were calculated for dissolution purpose. Distilled water was used as dissolution media where 900 ml of it was taken in each dissolution basket at a temperature of 37 ± 0.5°C and a paddle speed of 75 rpm. The fixed amount of solid dispersion from each batch was weighed and transferred in each dissolution basket. The dissolution was carried out for 60 min and 10 ml sample was withdrawn at predetermined intervals of 5, 10, 15, 20, 30, 40, 50 & 60 min. The sink condition was maintained using 10 ml fresh distilled water every time. Dissolution samples were filtered each time with syringe filter (0.45 µm) and were kept in a test tube. The dissolution samples were then analyzed spectrophotometrically by UV-VIS spectrophotometer (UV-mini-1240, SHIMADZU CORP, Kyoto, Japan) at 288 nm.

Results and Discussion

In vitro release study of carbamazepine from solid dispersion by physical mixing, fusion and solvent evaporation method: It was found that the dissolution rate of carbamazepine increased with the increasing amount of hydrophilic carriers in physical mixture batches. This was due to the increase in solubility of drug by the presence of hydrophilic carrier surrounding the drug particle. The formulation of the physical mixing F1, F2, F3 and F4 showed about 39.52, 43.11, 50.29 and 53.89% respectively for 60 minutes (Figure 1).

The formulations of the fusion method F1, F2, F3, F4, F5, F6, F7, F8 and F9 showed about 61.07, 64.67, 68.26, 73.65, 79.04, 82.63, 91.61, 87.48 and 95.20% release respectively for 60 minutes (Figure 2). The formulations of the solvent evaporation method F1, F2, F3, F4, F5, F6, F7, F8, F9 showed about 91.61, 95.20, 97, 98.80, 84.43, 93.41, 75.44, 71.85 and 80.83% of release respectively for 60 minutes (Figure 3).

Table 3. Correlation coefficient (R^2) values for the formulation of physical mixing method.

Product	Correlation coefficient (R^2) value			
Formulation	Zero order	First order Plot	Hixon Crowel Plot	Higuchi Plot
F1	0.967	0.942	0.747	0.984
F2	0.988	0.931	0.740	0.984
F3	0.977	0.954	0.693	0.980
F4	0.960	0.969	0.670	0.986

Table 4. Correlation coefficient (R^2) values for the formulation of fusion method.

Product	Correlation coefficient (R^2) value			
Formulation	Zero order	First order Plot	Hixon Crowel Plot	Higuchi Plot
F1	0.950	0.995	0.680	0.998
F2	0.973	0.952	0.727	0.995
F3	0.963	0.944	0.737	0.995
F4	0.970	0.959	0.713	0.995
F5	0.915	0.962	0.650	0.985
F6	0.901	0.642	0.953	0.980
F7	0.942	0.962	0.672	0.976
F8	0.935	0963	0.657	0.980
F9	0.980	0.930	0.762	0.988

Table 5. Correlation coefficient (R^2) values for the formulation of solvent evaporation method.

Product	Correlation coefficient (R^2) value			
Formulation	Zero order	First order Plot	Hixon Crowel Plot	Higuchi Plot
F1	0.924	0.920	0.630	0.963
F2	0.913	0.868	0.621	0.961
F3	0.953	0.979	0.605	0.988
F4	0.966	0.961	0.674	0.967
F5	0.928	0.895	0.621	0963
F6	0.918	0.990	0.658	0.959
F7	0.950	0.988	0.680	0.956
F8	0.907	0.806	0.622	0.96
F9	0953	0.979	0.605	0.988

The comparison of percent release among physical mixing, fusion and solvent evaporation method has been shown in figure 4. The correlation coefficients values of the trend lines of the graphs showed that formulation of Physical Mixing (F1-F4), Fusion (F1-F9) and Solvent evaporation (F1-F9) method best fits in Higuchian release pattern. The values of the correlation coefficients (R^2) for physical mixing, fusion and solvent evaporation method have been shown in the table 4, 5 and 6 respectively. It is difficult at this stage to explain in details the actual mechanism of release since, the polymer degradation starts during the dissolution period. However the possible reason of increased dissolution rate of carbamazepine was the use of surfactants for which the wettability and spreadability of the precipitated drug occur by reducing aggregations in the readily soluble state.

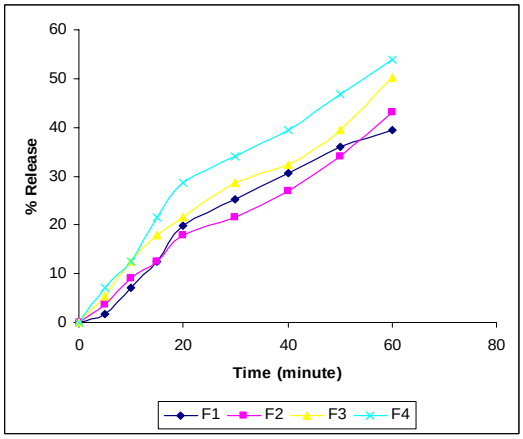

Figure 1. Percent release curve of carbamazepine with different excipients for the formulations F1 to F4 prepared by physical mixing method

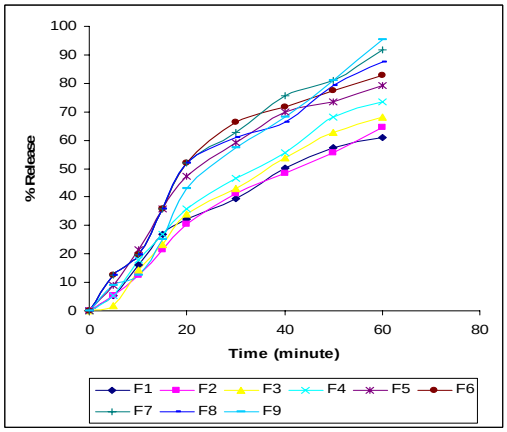

Figure 2. Percent release curve of carbamazepine with different excipients for the formulations F1 to F9 prepared by fusion method

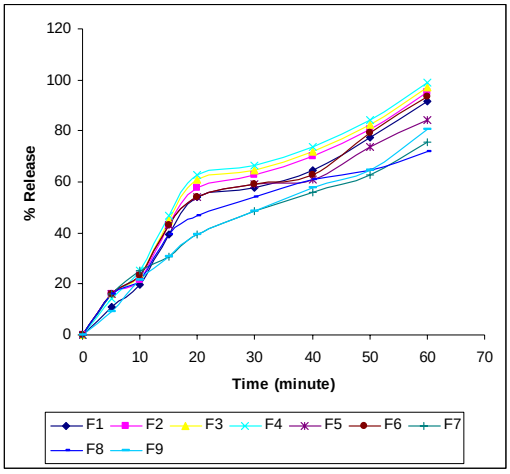

Figure 3. Percent release curve of carbamazepine with different excipients for the formulations F1 to F9 prepared by solvent evaporation method.

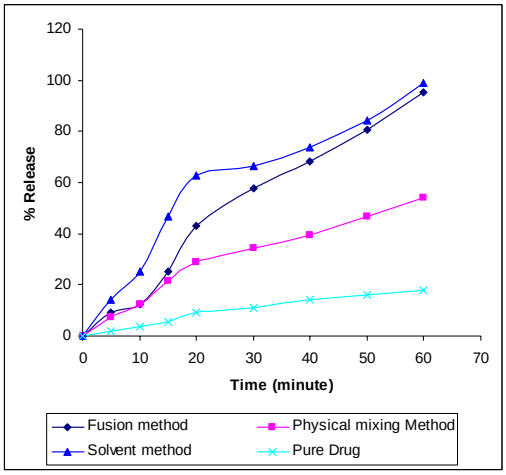

Figure 4. Comparison different percent release curves of Carbamazepine with different formulation methods

Conclusion

Carbamazepine is a poorly water soluble drug. Among the various approaches to improve the dissolution of poorly water soluble drugs, the preparation of physical mixing, fusion and solvent evaporation method have been proven to be very successful. In this study, PEG-6000, PVP-K-30, HPMC, poloxamer and sodium lauryl sulphate were used in the preparation of solid dispersion of carbamazepine to increase dissolution. The formulations were prepared at different ratios of drug and polymers. *In vitro* dissolution studies have shown significant increase in the dissolution of carbamazepine when PEG 6000 was used in the preparation of powder in physical mixing, fusion method and solvent evaporation method. PVP K30, sodium lauryl sulphate and Poloxamer also enhanced the solubility of carbamazepine as compared to the pure drug. On the contrary, the present study has shown that dissolution rate of the solid dispersion by solvent evaporation method was highest whereas dissolution of drug by fusion method was higher than by physical mixing method. In conclusion it can be mentioned that PEG 6000, Poloxamer 407 and PVP K30 can be used to improve the dissolution of carbamazepine in which the vehicles may act here as dispersing or emulsifying agents for the liberated drug, thus preventing the formation of any water-insoluble surface layers.

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