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COMPARATIVE STUDY OF DIFFERENT APPROACHES USED FOR SOLUBILITY ENHANCEMENT OF POORLY WATER SOLUBLE DRUGS

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Abstract

Albendazole, a benzimidazole derivative with broad spectrum of activity against human and animal helminth parasites, has very low oral bioavailability as it is a poorly soluble drug. The aim of this work was to improve the solubility of albendazole by using solvent evaporation method, with certain hydrophilic polymers such as polyvinyl pyrrolidone, mannitol, polyethylene glycol and by using hydrotropic solublization method with urea, sodium citrate and sodium benzoate as excipients. Solid dispersion as a dosage form has been established a superior option for the drugs having poor aqueous solubility while hydrotropy is one of the important solubility enhancement techniques that can be used to enhance solubilisation of poorly water soluble drugs in folds by using various hydrotropic agents. Mean saturated solubility of pure drug was found to be 0.31 µg/ml. Solid dispersion prepared with polyvinyl pyrrolidone had shown maximum solubility enhancement with solubility of 48.21 µg/ml as compare to polyethylene glycol and mannitol. While sodium citrate as hydrotropic agent had shown maximum solubility enhancement with solubility of 18.34 µg/ml as compare to urea and sodium benzoate. So the study concluded that formulating solid dispersion is better than hydrotropic solubilization method for solubility enhancement of drugs.

Keywords: Solubility enhancement, Solid dispersion, Hydrotropy, Albendazole, Solvent evaporation.

INTRODUCTION

The important phenomenon in pharmaceutical formulation is "solubility" which plays very effective and significant role in the formulation of various dosage forms. The solubility behaviour of drugs remains one of the most exigent aspects in formulation development. These days, the number of new chemical entities has dramatically increased having hiccups of poor solubility and poor permeability.[1] Solubility of a compound in a particular solvent is defined as the concentration of a solute in a saturated solution at a certain temperature. Solubilization of poorly soluble drugs is a frequently encountered challenge in screening studies of new chemical entities as well as in formulation design and development. A number of methodologies can be adapted to improve solubilization of poor water soluble drug and further to improve its bioavailability.[2] Solid dispersions in water-soluble carriers have engrossed considerable interest as a means of improving the dissolution rate and bioavailability of hydrophobic drugs. Although solid dispersions have tremendous potential for improving drug solubility and only a few marketed products using this approach.[1] There are various methods available to improve the solubility of the new drug in which solid dispersion emerged promising.[3] A Solid dispersion generally composed of two components- the drug and the polymer matrix. This article is intended to combine recent literature on solid dispersion technology for solubility enhancement with special emphasis on mechanism responsible for the same by solid dispersion and hydrotropy. The solubility of a drug is a key determinant of its oral bioavailability and permeability. There have always been certain drugs for which solubility has presented a challenge to the development of a suitable formulation for oral administration. Examples such as albendazole, mefanamic acid, levofloxacin etc immediately comes to mind. With the recent advent of high throughput screening of potential therapeutic agents, the number of poorly soluble drug candidates has risen sharply and the formulation of poorly soluble compounds is the greatest challenges to formulation scientists in the pharmaceutical industry. Therefore formulation approaches are being explored to enhance bioavailability of poorly water-soluble drugs. One such formulation approach that has been shown to significantly enhance absorption of such drugs is to formulate solid dispersion. The solid dispersions prepared by employing water soluble carrier are soft and tacky mass which is hard to handle. Various formulation parameters that play a crucial role for successful formulation are aqueous ambient temperature and humidity, photo stability, compatibility with solvents and excipients etc. Of these, solubility is the most important property for developing formulations.[1] Various hydrophilic carriers such as polyethylene

glycol [PEG], polyvinylpyrrolidone [PVP], hydroxypropyl cellulose, hydroxypropylmethyl cellulose, gums, sugar, mannitol, urea, hydroxypropylmethyl cellulose phthalate, gelucires, eudragits chitosan have been investigated for improvement of dissolution characteristics and bioavailability of poorly aqueous soluble drugs. Hydrophilic swellable polymers viz.,sodium carboxymethyl cellulose, sodium starch glycolate and pregelatinized starch are also used.

Albendazole (ABZ), methyl [5- (propylthio)-1-H-benzimidazol-2yl] carbamate, is a benzimidazol derivative with abroad spectrum of activity against human and animal helminth parasites. ABZ is effective in the treatment of echinococcosis, hydrated cysts and neurocysticercosis . ABZ is a poorly water-soluble drug (0.2 ug/ ml in water at 25 oC) Consequently, it is poorly absorbed from the gastrointestinal tract (< 5%) and it has low oral bioavailability. This property is a major disadvantage for the use of ABZ in the treatment of systemic helminthiasis. Furthermore, the lack of water solubility reduces flexibility for ABZ formulation and administration.[4] Therefore, the overcome of poor aqueous solubility of ABZ is an important goal. Different efforts have been made to enhance ABZ water solubility and dissolution rate such as preparation of oil in water emulsion, incorporation into liposomes, complexation with cyclodextrins, and preparation of solid dispersions. Moreover, increased systemic bioavailability of albendazole was reported when the drug co-administered with a fatty meal, fruit juice, cosolvent, or with surfactants. Solvent evaporation and hydrotropy is the most promising technique for this.

Hydrotrophy

Hydrotrophy is a solubilization process whereby addition of a large amount of second solute results in an increase in the aqueous solubility of another solute. Hydrotrophy designate the increase in solubility in water due to the presence of large amount of additives. The mechanism by which it improves solubility is more closely related to complexation involving a weak interaction between the hydrotropic agents like sodium benzoate, sodium acetate, urea and the poorly soluble drugs. Solute consists of alkali metal salts of various organic acids. Hydrotropic agents are ionic organic salts. Additives or salts that increase solubility in given solvent are said to “salt in” the solute and those salts that decrease solubility “salt out” the solute. Several salts with large anions or cations that are themselves very soluble in water result in “salting in” of non electrolytes called “hydrotropic salts” a phenomenon known as “hydrotropism”. Hydrotropic solutions do not show colloidal properties and involve a weak interaction between the hydrotropic agent and solute.[2]

CARRIERS

Polyethylene glycol (PEG)

Polyethylene glycols (PEG) are polymers of ethyleneoxide, with a molecular weight (MW) usually falling in the range 200-300000. For the manufacture of solid dispersions and solutions, PEGs with molecular weights of 1500-20 000 are usually employed. A meticulous advantage of PEGs for the solid dispersions is that they have good solubility in numerous organic solvents.[3]

Polyvinylpyrrolidone (PVP)

Polymerization of vinylpyrrolidone leads to polyvinylpyrrolidone (PVP) of molecular weights ranging from 2500 to 3000 000. These can be classified according to the K value, which is calculated using Fikentscher's equation. The aqueous solubility of the PVPs becomes poorer with increasing chain length and a further disadvantage of the high MW PVPs is their much higher viscosity at a given concentration.[3]

Urea

Urea is the end product of human protein metabolism, has a light diuretic effect and is regarded as non-toxic. Its solubility in water is greater than 1 and it also reveals good solubility in several common organic solvents. In one of the first bioavailability studies of solid dispersions, it was shown that sulphathiazole was better absorbed in rabbits when given as a eutectic with urea.[3]

EXPERIMENTAL

Solubility determination: To obtain solubility of the drug, it was added in excess amount in a beaker containing 10 ml of distilled water. Drug was added intermittently until saturation point reaches and precipitation occurs. It was kept for 24 hrs and sonicated. The resultant solution was filtered through 0.45 μm membrane filter. This filtrate was analysed by ultraviolet spectrophotometer at 298nm.

Formulation of solid dispersion using solvent evaporation method

The first step in the solvent evaporation method is, preparation of a solution containing both matrix material and drug. The second step involves the removal of solvent(s) resulting in formation of a solid dispersion. Accurately weighed 1g drug was dissolved in 10ml acetone to get a clear solution in a 100ml Round bottom Flask. Excipient used were PEG, PVP and mannitol in 1:1, 1:2 and 1:3 ratio, which were then added and dispersed. The solvent mixture

was removed by evaporation at 50°C while mixing content. The mass obtained was pulverized, mixed and then passed through sieve number 60.

Hydrotropic solid dispersion method [5]

For preparation of hydrotropic solid dispersion, accurately weighed urea, sodium benzoate, sodium citrates were taken in a beaker and were mixed properly. Then, minimum possible quantity of warm purified water sufficient to dissolve the above mixture was added (because lesser the amount of water lesser will be the time required to evaporate it and chemical stability of drug may not be affected adversely).

Dissolution of the hydrotropic mixture was facilitated by agitation of a Teflon coated magnetic rice bead on a high-speed magnetic stirrer. After complete dissolution of hydrotropic mixture, albendazole was dissolved in the above solution and temperature was maintained in the range of 55-60° so as to facilitate the evaporation of water. As evaporation proceeded, speed of bead automatically decreased and it stopped stirring when most of the water was evaporated, thus indicating the formation of solid dispersion (wet). The wet solid dispersion thus obtained were spread on several watch glasses and the watch glasses were kept in hot air dry oven maintained at 50±2° so that remaining moisture could also be evaporated easily and a constant weight with no further weight loss (due to evaporation) could be obtained. After complete drying, solid dispersions were crushed using a glass pestle mortar and passed through sieve # 60 and were finally stored in an airtight glass bottle.

RESULTS AND DISCUSSIONS

The solubility of drug was studied and the results are summarized in Table 1.The saturated solubility was found to be 0.031 ug/ml.

Table 1: Solubility of drug in distilled water

S. No.	Drug	Saturated solubility (µg/ml)			Mean saturated solubility ± SD (µg/ml)
		S1	S2	S3	
01	Albendazole	0.33	0.31	0.30	0.31±0.015

Different ratios of drug and excipients were taken in solvent evaporation for solid dispersion as well as hydrotropic solubilization method. In solvent evaporation method, as excipient concentration is increased as compare to drug in different ratio, we have seen different solubility pattern for each of the excipient.

As the concentration of excipient increased, solubility was found to be increased with mannitol, decreased with PVP and increased, reached to maximum then decreased with PEG.

Solubility characteristics of drug with solvent evaporation technique using carriers PEG, PVP and Mannitol are represented in table 2, 3 and 4. *All values are expressed as mean ± standard deviation, n=3.*

Table 2: Solubility characteristics of drug by solvent evaporation method using PEG.

S. No.	Carrier	Drug excipient ratio	Saturated solubility (µg/ml)			Mean Saturated solubility ± SD (µg/ml)
			S1	S2	S3	
01	PEG	1:1	18.63	18.00	18.9	18.51±0.46
		1:2	22.91	22.70	22.45	22.68±0.23
		1:3	14.25	14.40	14.00	14.23±0.20

Table 3: Solubility characteristics of drug by solvent evaporation method using PVP.

S. No.	Carrier	Drug excipient ratio	Saturated solubility (µg/ml)			Mean Saturated solubility ± SD (µg/ml)
			S1	S2	S3	
01	PVP	1:1	48.53	48.11	48.00	48.21±0.27
		1:2	43.50	42.70	43.11	43.10±0.4
		1:3	43.16	40.52	41.40	41.69±1.34

Table 4: Solubility characteristics of drug by solvent evaporation method using Mannitol

S. No.	Carrier	Drug excipient ratio	Saturated solubility (µg/ml)			Mean Saturated solubility ± SD (µg/ml)
			S1	S2	S3	
01	Mannitol	1:1	6.00	6.24	6.54	6.26±0.27
		1:2	8.66	8.52	8.44	8.54±0.11
		1:3	9.33	9.45	9.72	9.50±0.19

In hydrotropic solubilization method, as the concentration of excipient increased, solubility was found to be increased with urea and sodium benzoate while solubility increased, reached to maximum then decreased with sodium citrate.

Solubility characteristics of drug using carriers urea, sodium citrate and sodium benzoate is represented in table 5, 6 and 7.

Table 5: Solubility characteristics of drug by hydrotropic solubilisation method using urea

S. No.	Carrier	Drug excipient ratio	Saturated solubility (µg/ml)			Mean Saturated solubility ± SD (µg/ml)
			S1	S2	S3	
01	Urea	1:1	2.91	3.00	3.20	3.03±0.14
		1:2	8.60	8.00	8.24	8.28±0.30
		1:3	10.2	10.00	9.80	10.0±0.2

Table 6: Solubility characteristics of drug by hydrotropic solubilisation method using sodium citrate

S. No.	Carrier	Drug excipient ratio	Saturated solubility (µg/ml)			Mean Saturated solubility ± SD (µg/ml)
			S1	S2	S3	
01	Sodium citrate	1:1	5.16	5.24	5.55	5.31±0.20
		1:2	18.16	18.34	18.52	18.34±0.18
		1:3	9.68	9.22	9.42	9.44±0.23

Table 7: Solubility characteristics of drug by hydrotropic solubilisation method using sodium benzoate

S. No.	Carrier	Drug excipient ratio	Saturated solubility (µg/ml)			Mean Saturated solubility ± SD (µg/ml)
			S1	S2	S3	
01	Sodium benzoate	1:1	6.33	6.24	6.56	6.37±0.16
		1:2	7.83	7.54	7.66	7.67±0.15
		1:3	15.66	15.92	15.42	15.66±0.25

So Solid dispersion prepared with polyvinyl pyrrolidone had shown maximum solubility enhancement with solubility of 48.21 µg/ml as compare to polyethylene glycol and mannitol. While sodium citrate as hydrotropic agent had shown maximum solubility enhancement with solubility of 18.34 µg/ml as compare to urea and sodium benzoate

CONCLUSION

The results shown that the prepared solid dispersions has better solubility than the pure drug because complexation of drug and carrier. Therefore to improve absorption, oral

bioavailiability and to enhance pharmacokinetic profile, the solid dispersion can be a suitable alternative to other available dosage form.

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REFERENCES

1 Nikghalb LA, Singh G, Singh G, Kahkeshan KF, Solid Dispersion: Methods and Polymers to increase the solubility of poorly soluble drugs, J Appl Pharm Sci, 2012; 2(10):170-175.

2 Chaudhary A, Nagaich U, Gulati N, Sharma VK, Khosa RL, Enhancement of solubilization and bioavailability of poorly soluble drugs by physical and chemical modifications: A recent review, J Adv Pharm Edu Res, 2012; 2 (1): 32-67.

3 Sharma A, Jain CP, Solid dispersion: A promising technique to enhance solubility of poorly water soluble drug, Int J Drug Del, 2011; 3: 149-170.

4 Alanazi FK, El-Badry M, Ahmed MO, Alsarra IA, Improvement of Albendazole Dissolution by Preparing Microparticles Using Spray-Drying Technique, Scientia Pharmaceutica, 2007; 75: 63-79.

5 Maheswari RK, Jagwani Y, Mixed Hydrotropy: Novel Science of Solubility Enhancement, Ind J Pharm Sci, 2011; March-April: 179-183.

6 Dahima R., Gangwal S., A comparative study of solubility enhancement of enalapril using formulation of solid dispersion and using hydrotropic solubilization technique, Res J Pharm, Biol Chem Sci, 2013; 4(4): 1301-05.