RESEARCH ARTICLE
Department of Pharmaceutics

Rahman et.al / UJPSR / 2 (1), 2016, 1-8
e ISSN: 2454-3764
Print ISSN: 2454-3756

ANALYZE THE EFFECT OF POLYETHYLENE GLYCOL - 6000 AND AVICEL ON POORLY WATER SOLUBLE DRUG ALBENDAZOLE BY SOLID DISPERSION METHOD

[1]Md. Habibur Rahman*, [2]Samira Yesmin, [3]Md. Arifur Rahman Chowdhury, [1]Kuntal Kumar Das, [4]Md. Mizanur Rahman, [5]Nadezda Al Azad

[1]One Pharma Ltd, Executive production, Bogra, ***BANGLADESH***
[2]Ego Pharma Ltd, Executive Quality Control, ***BANGLADESH***
[3]South-East University, ***BANGLADESH***
[4]Nipa Pharmaceutical Ltd., Executive Quality Control, ***BANGLADESH***
5One Pharma Ltd, Executive product Development, Bogra, ***BANGLADESH***

ARTICLE INFO:
Article history:
Received: 1 December 2015
Received in revised form:
30 December 2015
Accepted: 10 January 2016
Available online: 10 May 2016

Corresponding Author:
Md. Habibur Rahman
One Pharma Ltd,
Executive production
Bogra, ***BANGLADESH***
Email: pharmacisthabib@gmail.com
Phone: +8801736770093

Abstract

This article shows by using solid dispersion method how the solubility of Albendazole depends on polyethylene glycol and avicel. The term solid dispersion refers to the dispersion of one or more active ingredient in an inert carrier or matrix at solid state prepared by melting (fusion), solvent, or the melting solvent method. The therapeutic effect of drugs depends on the drug concentration at the site of action. The absorption of the drug into the systemic circulation is a prerequisite to reach the site of action for all drugs, except those drugs that are applied at the site of action, or those that are intravenously injected. After oral administration (gastrointestinal route), many factors determine the bioavailability (fraction of drug reaching the systemic circulation). In recent years, a great deal of knowledge has been accumulated about solid dispersion technology, but their commercial application is limited. From the study of Albendazole was performed to improve the % release of drug to increase polymers ratio, which found to be prepared solid dispersion by using fusion method. From Fig-3.5, PA-5 the polymer ratio (Albendazole: PEG 6000: Avicel = 1:4:4) gave more drug release 65.10% within 1 hour than the other polymer ratio (4:1:1, 2:1:1, 1:1:1, 1:2:2) & the physical mixture & pure drug of Albendazole.

Key words

Solid dispersion method, Polyethylene glycol, Avicel, Albendazole.

INTRODUCTION

Albendazole is broad-spectrum anthelmintic efficiency with low toxicity. It used to drive the clinical roundworm, pinworm, tapeworm, whipworm, hookworm, round worm manure and so on. Metabolism in the body sulfoxide or sulfone class, the inhibition of parasite uptake of glucose, resulting in parasite glycogen depletion, or inhibition of fumarate reductase system that prevents the production of ATP, the parasite cannot survive and reproduce **[1]**. Albendazole, marketed as Albenza, Eskazole, Zentel, Andazole and Alworm, is a member of the benzimidazomol compounds used as a drug indicated for the treatment of a variety of worm infestations. Although this use is widespread in the United Stated, the U.S Food and Drug Administration (FDA) have not approved Albendazole for this indication.

Drug Characteristic

Albendazole is white or almost white powder, odorless, tasteless, and insoluble in water, slightly soluble in acetone or chloroform. On selective and irreversible intestinal nematode parasites of the

Rahman et.al / UJPSR / 2 (1), 2016, 1-8
e ISSN: 2454-3764
Print ISSN: 2454-3756

intestinal wall to inhibit the cytoplasmic microtubule polymerization, blocking its uptake of various nutrients and glucose absorption, leading to insect endogenous glycogen depletion, and inhibition of fumarate reduction enzyme system, to prevent the production of ATP, resulting in parasites cannot survive and reproduce. With mebendazole similar, the goods can cause intestinal parasites cytoplasmic microtubules degeneration, and its tubule binding, causing blockage of intracellular transport, resulting in golgi accumulation of endocrine granules, the cytoplasm gradually dissolved, absorption cells completely denatured, death caused by parasites. This product has completely killed the hook and whip eggs and some eggs to kill the role of Ascaris eggs. In addition to get rid of parasites on animals to kill a variety of nematodes, tapeworm and cysticercosis are also evident on the kill and get rid of role. Toxicology tests showed that the toxicity of the product, safety. Mouse oral LD50 is greater than 800mg/kg, the maximum tolerated dose in dogs oral 400mg/kg or more. The drugs on male reproductive function in mice had no effect on female mice and no teratogenic effects in female rats and female rabbits, application of larger doses (30mg/kg / day), it can absorb and bone of fetal malformations **[2]**.

Major uses

It is effective first line of treatment against:

Flatwarm

Flukes/trematodes

Fasciolosis

Tapeworm/cestodes

Cysticercosis

Nematodes

Enterobiasis (pinwarm infection)

Trichuriasis (whipworm infection)

Ascariasis

Hookwarm **[3]**

Mode of action

Albendazole causes degenerative alterations in the tegument and intestinal cells of the worm by binding to the colchicine-sensitive site of tubulin, thus inhibiting its polymerization or assembly into microtubules. The loss of the cytoplasmic microtubules leads to impaired uptake of glucose by the larval and adult stages of the susceptible parasites, and depletes their glycogen stores. Degenerative changes in the endoplasmic reticulum, the mitochondria of the germinal layer, and the subsequent release of lysosomes result in decreased production of adenosine triphosphate (ATP) **[4]**, which is the energy required for the survival of the helminth. Due to diminished energy production, the parasite is immobilized and eventually dies. Albendazole also has been shown to inhibit the enzyme fumarate reductase, which is helminth -specific. This action may be considered secondary to the effect on the microtubules due to the decreased absorption of glucose. This action occurs in the presence of reduced amounts of nicotinamide-adenine di nucleotide in reduced form (NADH), which is a coenzyme involved in many cellular oxidation-reduction reactions. Albendazole has larvicidal effects in necarotiasis and ovicidal effects in ascariasis, ancylostomiasis, and trichinosis.

Side effects

Albendazole may cause abdominal pain, dizziness, headache, fever, nausea, vomiting, or temporary hair loss. In rare cases it may cause persistent sore throat, severe headache, seizures, vision problems, yellowing eyes or skin, dark urine, stomach pain, easy bruising, mental/mood changes, very stiff neck, change in amount of urine. Elevation of liver enzymes during treatment is a common side effect, but in rare cases there have also been reports of acute liver failure. Allergic reactions are also possible. Rarely Albendazole has been reported to cause marrow suppression, agranulocytosis or aplastic anemia which may be permanent. The risk of developing this side effect seems to be increased in patients with liver disease, including echinococcal cysts. Because of this dangerous side effect it is important to regularly monitor complete blood counts. D (Australia) - Do not take when pregnant, and do not become pregnant for one month after taking this drug. Pharmacokinetic studies have shown that trace amounts of Albendazole appears in semen. Given this potential for teratogenecity, the manufacturers advise that the male sexual partner should also use adequate protection **[5]**.

Preparation of solid dispersions

Various preparation methods for solid dispersions have been reported in literature. These methods deal with the challenge of mixing a matrix and a drug, preferably on a molecular level, while matrix and drug are generally poorly miscible. During many of the preparation techniques, de-mixing (partially or complete), and formation of different phases is observed. Phase separations like crystallization or formation of amorphous drug clusters are difficult to control and therefore unwanted. It was already recognized in one of the first studies on solid dispersions that the extent of phase separation can be minimized by a rapid cooling procedure **[6]**.Generally, phase separation can be prevented by maintaining a low molecular mobility of matrix and drug during preparation. On the other hand, phase separation is prevented by maintaining

Rahman et.al / UJPSR / 2 (1), 2016, 1-8
e ISSN: 2454-3764
Print ISSN: 2454-3756

the driving force for phase separation low for example by keeping the mixture at an elevated temperature thereby maintaining sufficient miscibility for as long as possible.

Fusion method

The fusion method is sometimes referred to as the melt method, which is correct only when the starting materials are crystalline. Therefore, the more general term fusion method is preferred. The first solid dispersions created for pharmaceutical applications were prepared by the fusion method. The dispersion consisted of sulfathiazole and urea as a matrix **[6]** which were melted using a physical mixture at the eutectic composition, followed by a cooling step. The eutectic composition was chosen to obtain simultaneous crystallization of drug and matrix during cooling. This procedure resulted in solid dispersions of type I. Polyethylene glycol (PEG) is a hydrophilic polymer often used to prepare solid dispersions with the fusion method. This often results in solid dispersions of type III since many drugs are incorporated as separate molecules in the helical structure present in a crystalline PEG.

Hot melt extrusion

Melt extrusion is essentially the same as the fusion method except that intense mixing of the components is induced by the extruder. When compared to melting in a vessel, the product stability and dissolution are similar **[7]**, but melt extrusion offers the potential to shape the heated drug-matrix mixture into implants, ophthalmic inserts, or oral dosage forms [8]. Just like in the traditional fusion process, miscibility of drug and matrix can be problem. Solubility parameters are investigated to predict the solid state miscibility and to select matrices suitable for melt extrusion. High shear forces resulting in high local temperatures in the extruder are a problem for heat sensitive materials **[9, 10]**. However, compared to the traditional fusion method, this technique offers the possibility of continuous production, which makes it suitable for large-scale production. Furthermore, the product is easier to handle because at the outlet of the extruder the shape can be adapted to the next processing step without grinding.

Solvent method

The first step in the solvent method is the 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. Mixing at the molecular level is preferred, because this leads to optimal dissolution properties. Using the solvent method, the pharmaceutical engineer faces two challenges. The first challenge is to mix both drug and matrix in one solution, which is difficult when they differ significantly in polarity. To minimize the drug particle size in the solid dispersion, the drug and matrix have to be dispersed in the solvent as fine as possible preferably drug and matrix material are in the dissolved state in one solution. Various strategies have been applied to dissolve the lipophilic drug and hydrophilic matrix material together in one solution. Low drug concentrations are used to dissolve both drug and matrix material in water **[11]** but this requires evaporation of tremendous amounts of solvent, making the process expensive and impractical. Solubilizers like cyclodextrins or surfactants like Tween80® increase the aqueous solubility of the drug substantially. However, the amount of solubilizers or surfactants in the final product is often eminent. This results in solid dispersions that, to a significant extent, consist of solubilisers or surfactants, materials that significantly change the physical properties of the matrix (e.g., decrease of Tg). Moreover, only dosage forms with low drug loads are possible. In addition, they are not always tolerated well in the body or may even be toxic. Chloroform **[12]** or dichloromethane have been used to dissolve both drug and PVP as matrix simultaneously.

These solvents are used also in other preparation methods. This is depicted in fig. 1.

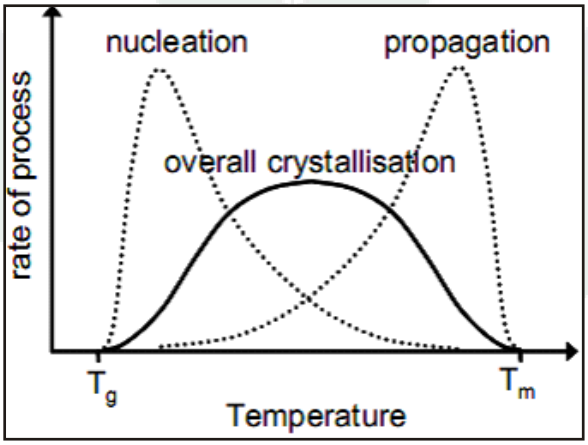

Fig. 1: Overall crystallization rate as a function of temperature. TG is the glass transition temperature and Tm is the melting temperature.

Rahman et.al / UJPSR / 2 (1), 2016, 1-8
e ISSN: 2454-3764
Print ISSN: 2454-3756

Supercritical fluid methods

Supercritical fluid methods are mostly applied with carbon dioxide (CO2), which is used as either a solvent for drug and matrix or as an anti-solvent. When supercritical CO2 is used as solvent, matrix and drug are dissolved and sprayed through a nozzle, into an expansion vessel with lower pressure and particles are immediately formed. The adiabatic expansion of the mixture results in rapid cooling. This technique does not require the use of organic solvents and since CO2 is considered environmentally friendly, this technique is referred to as 'solvent free'. The technique is known as Rapid Expansion of Supercritical Solution (RESS). However, the application of this technique is very limited, because the solubility in CO2 of most pharmaceutical compounds is very low (<0.01wt-%) [13] and decreases with increasing polarity. Therefore, scaling up this process to kilogram-scale will be impractical. The general term for this process is Precipitation with Compressed Anti-Solvent (PCA) [14]. More specific examples of PCA are Supercritical Anti Solvent (SAS) when supercritical CO2 is used, or Aerosol Solvent Extraction System (ASES), and Solution Enhanced Dispersion by Supercritical fluids (SEDS). However, as with the other solvent techniques described in the previous section, the critical step in these precipitation techniques might be the dissolution of drug and matrix in one solution. The use of water is limited, because the water solubility in compressed CO2 is limited **[15]**. Usually organic solvents like dichloromethane or methanol have to be applied to dissolve both drug and matrix **[16]**. In another process called supercritical fluid impregnation.

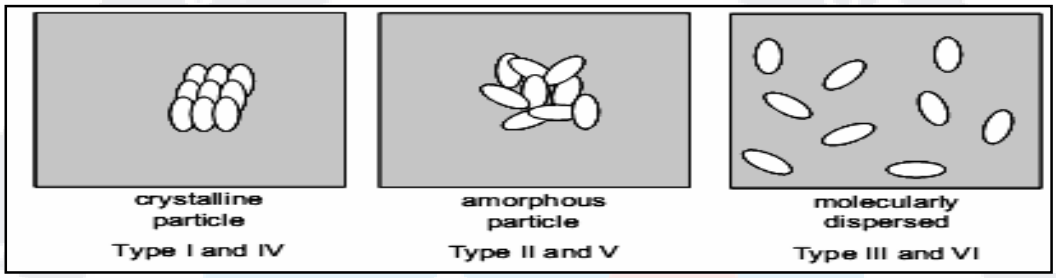

Fig. 2: Schematic representation of three modes of incorporation of the drug in a solid dispersion

MATERIALS AND METHODS

Table 1: List of chemicals, Equipments and instruments and apparatus

Chemicals	
Drug	Albendazole
Polymers	PEG 60000
	Avicel PH 101
Buffer	Di-Sodium hydrogen Phosphate
	Sodium di-hydrogen Phosphate

Preparation of Standard Curve

Standard curve of Albendazole gave repression equation Y= 0.0205+0.4151 with a confidence level of R= 0.9742

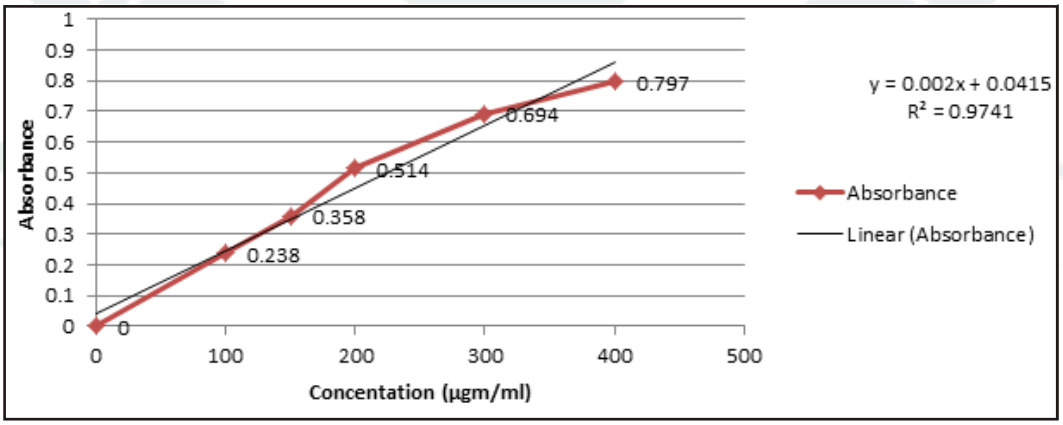

Fig. 3: Standard curve of Albendazole

Rahman et.al / UJPSR / 2 (1), 2016, 1-8
e ISSN: 2454-3764
Print ISSN: 2454-3756

Preparation of solid dispersion

For the preparation of solid dispersions of Albendazole fusion method was used. Dispersions systems by the fusion method were prepared by mixing the required amount of drug and polymer in glass vials. The mixture was then heated till it was completely melted. The temperature was maintained to a range of 80°C-90°C.Continuous stirring during the melting procedure prevented separation of the constituents. The melt was then rapidly solidified. The formulations were kept in desiccators'. The solidified mass was then crushed, size reduced in a mortar and pastel and sieved through a 150 micron sieve. Formulations were stored in glass vials and kept in desiccator. All vials were labeled with care. The required samples for dissolution studies were taken from the vials.

Preparation of solid dispersions of Albendazole using PEG 6000 & Avicel

Table 2: Different ratios of Albendazole and PEG 6000 & Avicel

Code	Polymers	Albendazole (mg)	PEG 6000 (mg)	Avicel (mg)	Albendazole: PEG 6000: Avicel
PA 1	Polyethylene glycol (PEG 6000) & Avicel	500	125	125	4:1:1
PA 2		500	250	250	2:1:1
PA 3		500	500	500	1:1:1
PA 4		500	1000	1000	1:2:2
PA 5		500	2000	2000	1:4:4

500 mg of Albendazole was weighed out using an electronic balance and taken in previously washed and cleaned moisture free glass vials. PEG 6000 & avicel was weighed as shown in the table. Albendazole heated in Bunsen Burner at a temperature range of 80°C-90°C until a clear solution was obtained. PEG 6000 was added to the clear solution after a few minutes Avicel was also added to the clear solution and heating was continued till a homogeneous mixture was obtained. Continuous stirring of the drug and polymer was ensured using a glass rod. As homogeneous mixture achieved the vial was taken out of the water. Stirring was continued and solid mass was obtained. The solid mass in the vial was kept in desiccators. After complete removal of moisture the solidified formulation was crushed in a mortar and pestle, size reduced and sieved through a 150 micron sieve. Formulations of Albendazole: PEG 6000: Avicel of different drug-polymer ratio (4:1:1, 2:1:1, 1:1:1, 1:2:2 and 1:4:4) were prepared. Finally all the formulations were transferred in glass vials and labeled accordingly (codes are shown in the table) and stored in a desiccator.

***In vitro* dissolution Study**

These studies were conducted at 37+0.5°C on an USP specification dissolution rate test type 2 apparatus (Paddle apparatus) with six sections assembly according to the USP 30 procedure (USP 30 and NF 25,2007). For in vitro dissolution studies, phosphate buffer pH 7.4 was used as dissolution media. Water-bath temperature was fixed & confirmed to be 37+0.5°C before starting the experiment. The medium was preheated to 37°C and then a quantity of 900 ml was added to ease vessel. The apparatus was then assembled and paddle rotation was started and adjusted at 50 rpm and the system was allowed to equilibrate for 15 minutes. After that the paddle rotations was stopped and fixed amounts of solid dispersion containing 50mg equivalent Albendazole from each batch were placed in the vessels. The apparatus was immediately operated at 50 rpm. Each vessel, vessel position and corresponding sample result were assigned the same code. The duration of the experiment was 60 minutes for each set of sample. 10ml of sample was withdrawn from the media at pre-determined intervals of 5, 15, 30, 60 minutes. Each & every time 10ml of dissolution sample was compensated by adding 10ml fresh phosphate buffer. The sample solutions were diluted and analyzed at 294 nm for Albendazole by UV spectrophotometer. The amount of drug present in the sample was calculated from calibration curve constructed from the standard solution of USP reference standard test drug.

Preparation of phosphate buffer pH 7.4

1.421gm di-sodium hydrogen phosphate and 0.227gm sodium di-hydrogen ortho phosphate were weighed out and dissolved in a small amount of distilled water, volume was adjusted to 1 litter with the same solvent to prepare I litter phosphate buffer. The pH of the buffer solution was adjusted using a pH meter.

Rahman et.al / UJPSR / 2 (1), 2016, 1-8
e ISSN: 2454-3764
Print ISSN: 2454-3756

RESULT AND DISCUSSION

After all of the experimental observation found some expected desired % release pattern from various ratio of polymers. For ease of comparison I used physical mixture, PEG6000 & Avicel and pure drug (Albendazole). The findings are presented as graphs and brief elaboration is given here.

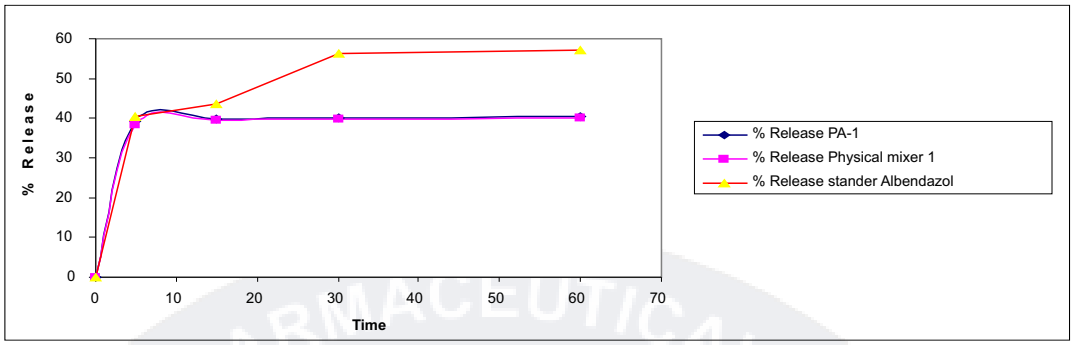

Fig 3.1: % Release of Albendazole from solid dispersion prepared in ratio Albendazole: PEG 6000: Avicel (4:1:1)

From Fig.3.1 it was found that solid dispersion prepared in a drug to polymer ratio (Albendazole: PEG 6000: Avicel = 4:1:1) gave 40.30% drug release within 1st hour. Whereas the physical mixture at the same ratio resulted in 40.00% drug release and pure drug of Albendazole 57.10%.So the release pattern is as bellow:

Pure Drug > Solid dispersion > Physical Mixture

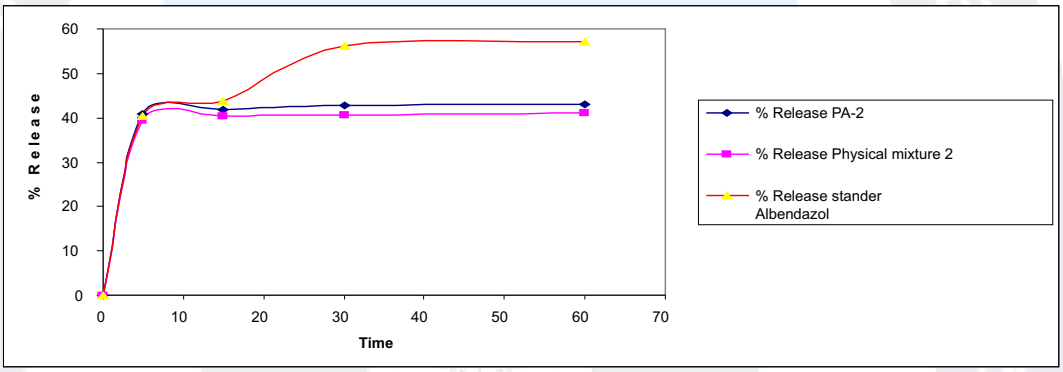

Fig: 3.2: % Release of Albendazole from solid dispersion prepared in ratio Albendazole: PEG 6000: Avicel (2:1:1)

From Fig. 3.2 it was found that solid dispersion prepared in a drug to polymer ratio (Albendazole: PEG 6000: Avicel = 2:1:1) gave 43.00% drug release within 1st hour. Whereas the physical mixture at the same ratio resulted in 41.00% drug release and pure drug of Albendazole 57.10%.So the release pattern is as bellow:

Pure Drug > Solid dispersion > Physical Mixture

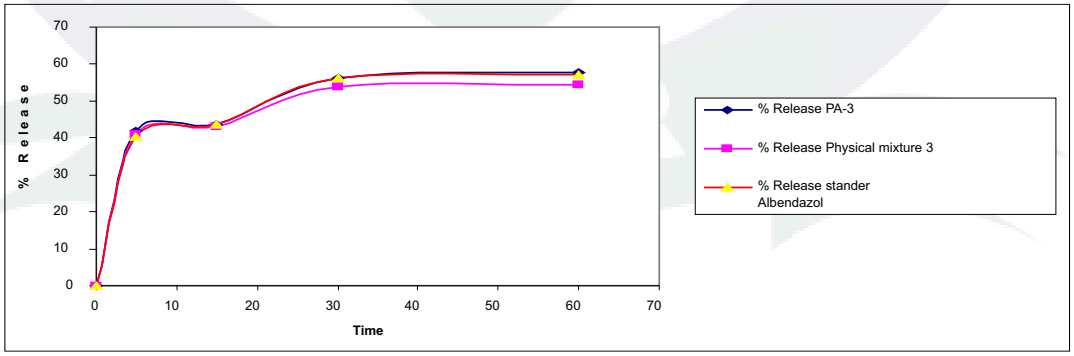

Fig: 3.3: % Release of Albendazole from solid dispersion prepared in ratio Albendazole: PEG 6000 : Avicel (1:1:1)

Rahman et.al / UJPSR / 2 (1), 2016, 1-8
e ISSN: 2454-3764
Print ISSN: 2454-3756

From Fig. 3.3 it was found that solid dispersion prepared in a drug to polymer ratio (Albendazole: PEG 6000: Avicel = 1:1:1) gave 57.60% drug release within 1st hour. Whereas the physical mixture at the same ratio resulted in 54.50% drug release and pure drug of Albendazole 57.10%.So the release pattern is as bellow:

Solid dispersion >Pure drug> Physical Mixture

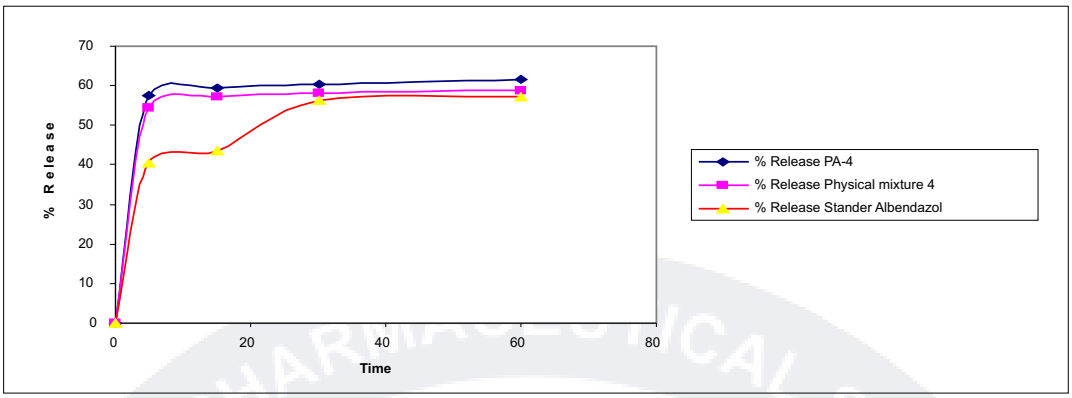

Fig. 3.4: % Release of Albendazole from solid dispersion prepared in ratio Albendazole: PEG 6000 : Avicel (1:2:2)

From Fig-3.4 it was found that solid dispersion prepared in a drug to polymer ratio (Albendazole: PEG 6000: Avicel = 1:2:2) gave 61.60% drug release within 1st hour. Whereas the physical mixture at the same ratio resulted in 58.70% drug release and pure drug of Albendazole 57.10%.So the release pattern is as bellow:
Solid dispersion > Physical Mixture > Pure Drug

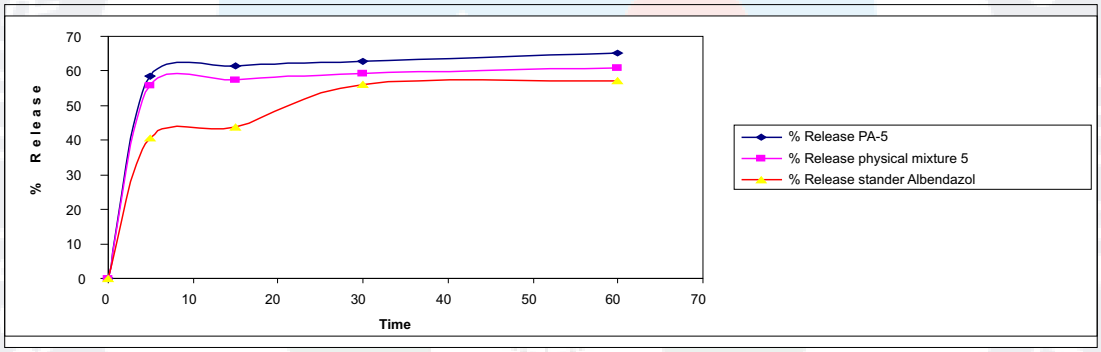

Fig.3. 5: % Release of Albendazole from solid dispersion prepared in ratio Albendazole: PEG 6000: Avicel (1:4:4)

From Fig.3.5 it was found that solid dispersion prepared in a drug to polymer ratio (Albendazole: PEG 6000: Avicel = 1:4:4) gave 65.10% drug release within 1st hour. Whereas the physical mixture at the same ratio resulted in 61.00% drug release and pure drug of Albendazole 57.10%.So the release pattern is as bellow:
Solid dispersion > Physical Mixture > Pure Drug

DISCUSSION

From Fig-3.4 & Fig-3.5 we found that the prepared solid dispersion offered more drug release than the physical mixture & pure drug of Albendazole. And from Fig-3.1, 3.2, 3.3 denoted PA-1, PA-2, PA-3 we found the drug release pattern was less than from physical mixture & pure drug of Albendazole. On the other hand, Fig-3.4, PA-4 in polymer ratio 1:2:2 offered drug release 61.60% & Fig-3.5,PA-5 in polymer ratio 1:4:4 offered drug release 65.10% within one hour. As a result it was cleared that to increase polymer ratio enhanced water solubility of poorly water soluble drug Albendazole by solid dispersion method.

Rahman et.al / UJPSR / 2 (1), 2016, 1-8
e ISSN: 2454-3764
Print ISSN: 2454-3756

CONCLUSION

Albendazole is a poorly water soluble drug to BCS class-2 drug. So, water solubility enhancement of this drug is a major challenge for the pharmaceutical scientist. Solid dispersion is a widely used method and nowadays in this systems have been realized as extremely useful tool in improving the dissolution properties of poorly water-soluble drugs of Biopharmaceutical Classification System class-2. In recent years, a great deal of knowledge has been accumulated about solid dispersion technology, but their commercial application is limited. From the study of Albendazole was performed to improve the % release of drug to increase polymers ratio, which found to be prepared solid dispersion by using fusion method. From Fig-3.5, PA-5 the polymer ratio (Albendazole: PEG 6000: Avicel = 1:4:4) gave more drug release 65.10% within 1 hour than the other polymer ratio (4:1:1, 2:1:1, 1:1:1, 1:2:2) & the physical mixture & pure drug of Albendazole. Finally, it was declared that increased the polymer ratio (PEG 6000: Avicel) improved water solubility on poorly water soluble drug Albendazole by solid dispersion method.

REFERENCES

1. *http://www.articlesbase.com/medicine-articles/the-description-of-Albendazolee-3598238.html*
2. *http://kbtips.com/v271/health/The-description-of-Albendazolee.html*
3. *Helminths: Intestinal nematode infection: Albendazolee". WHO Model Prescribing Information: Drugs Used in Parasitic Diseases - Second Edition. WHO. 1995. Retrieved 2015- 08-29.*
4. *https://www.parasitetesting.com/Albendazolee.cfm*
5. *"Albenza (Albendazolee) - Warnings and Precautions". Retrieved 9 March 2011.*
6. *Sekiguchi K and Obi N (1961). Studies on Absorption of Eutectic Mixture. I. A comparison of the behaviour of eutectic mixture of sulfathiazole and that of ordinary sulfathiazole in man. Chem. Pharm. Bull., 9: 866-872.*
7. *Forster A, Hempenstall J, Tucker I and Rades T (2001). The potential of small-scale fusion experiments and the Gordon-Taylor equation to predict the suitability of drug/polymer blends for melt extrusion. Drug Dev. Ind. Pharm., 27(6): 549-560.*
8. *Breitenbach J (2002). Melt extrusion: from process to drug delivery technology. Eur. J. Pharm. Biopharm., 54(2): 107-117.*
9. *Langer M, Höltje M, Urbanetz NA, Brandt B, Höltje HD and Lippold BC (2003). Investigations on the predictability of the formation of glassy solid solutions of drugs in sugar alcohols. Int. J. Pharm., 252(1-2): 167-179.*
10. *Forster A, Hempenstall J and Rades T (2001). Characterization of glass solutions of poorly watersoluble drugs produced by melt extrusion with hydrophilic amorphous polymers. J. Pharm. Pharmacol., 53(3): 303-315.*
11. *Orienti I, Bigucci F, Luppi B, Cerchiara T, Zuccari G, Giunchedi P and Zecchi V (2002). Polyvinyl alcohol substituted with triethylene glycol mono ethyl ether as a new material for preparation of solid dispersions of hydrophobic drugs. Eur. J. Pharm. Biopharm., 54(2): 229-233.*
12. *Betageri GV and Makarla KR (1995). Enhancement of dissolution of glyburide by solid dispersion and lyophilization techniques. Int. J. Pharm., 126: 155-160.*
13. *Palakodaty S and York P (1999). Phase behavioral effects on particle formation processes using supercritical fluids. Pharm. Res., 16(7): 976-985.*
14. *Subramaniam B, Rajewski RA and Snavely K (1997). Pharmaceutical processing with supercritical carbon dioxide. J. Pharm. Sci., 86(8): 885-890.*
15. *Sarkari M, Brown J, Chen X, Swinnea S, Williams RO (2002). Enhanced drug dissolution using evaporative precipitation into aqueous solution. Int. J. Pharm., 243(1-2): 17-31.*
16. *Sethia S and Squillante E (2003). Solid dispersions: revival with greater possibilities and applications in oral drug delivery. Crit. Rev. Ther. Drug Carrier Syst., 20(2-3): 215-247.*