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FORMULATION AND EVALUATION OF EFAVIRENZ EFFERVESCENT GRANULES

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ABSTRACT

The drug selected for the study was Efavirenz which is used in treatment of AIDS and belongs to BCS class II drug with poor aqueous solubility. Therefore the present study was planned to improve solubility and dissolution rate of Efavirenz through solid dispersion technique. Solid dispersions of Efavirenz were prepared using PVPK^{30}, starch as carrier in indifferent drug :carrier ratio 1:5, 1:10, 1:15 by employing solvent evaporation method. The prepared solid dispersion was evaluated for % drug content and saturation solubility studies. From the results of saturation solubility studies it was observed that there was decrease in solubility of drug as carrier concentration increase in physical mixtures containing starch but when compared with solid dispersion. The solubility increase 3 folds to thatpure drug with carrier concentration increases. While in case of PVPK30 in physical mixtures and solid dispersions as concentration increases, solubility also increases 3 folds to that of pure drug. These solid dispersion were used for preparation of effervescent granules by using citric acid, tartaric acid and sodium bicarbonate. These granules were evaluated for various physicochemical properties i.e., bulk density, tapped density, hausner's ratio, carr's index and angle of repose. The results were found to be within the prescribed limits indicating good flow property of granules. The prepared granules were also evaluated for %maisture content, % drug content and effervescence time and from the results the drug content was found to be in the range content among various formulations. The moisture content was found to be within the range of a minimum of 0.01 ±0.01 and maximum of 0.08 ±0.01 indicates the ability, free flow ability. From the results of the present study it can be concluded that the solubility of the drug can be significantly enhanced with the natural polymer as that of the synthetic polymer when compared to that of pure drug the order of increase in solubility is SDS 15> SDP15> PMS5> SDP10> PMP15> PMP10> SDS110> PMP5> SDS5> PMS10> PMS15. The order of increase in dissolution rate was found to be SDS15> SDS5> PMS5> PMS10> SDS10> PMS15> SDP15> SDP5> SDP10-> PMP5> PMP10> PMP15. Formulation containing 1:15 ratio of drug:starch is considered as best formulation as it has shown highest drug release in short time i.e., 99.96% in 3.30 min. Therefore starch can be successfully employed for developing effervescent granules of poorly soluble drugs like efavirenz with solid dispersion technique.

Key words: Efavirenz, solid dispersion technique, effervescent granules

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INTRODUCTION

As early as in 1960, Sekiguchi et al. developed the concept of solid dispersion to enhance absorption of

poorly water soluble drugs. It involved formation of eutectic mixtures of drugs with water soluble carriers by melting of their physical mixtures, and once the carriers dissolved, the drug precipitated in a finely divided state in water. Later, Goldberg et al. demonstrated that a certain fraction of the drug may also be molecularly dispersed in the matrix, forming solid solutions, while other investigators reported that the drug may be embedded in the matrix as amorphous materials. On the basis of these considerations, chiou and riegelman defined solid dispersion as "The dispersion of one or more active ingredients in an inert excipient or matrix, where the active ingredient could exist in finely crystalline, solubilized, or amorphous states".

Compared to conventional tablet and capsule dosage forms, solid dispersion formulations are relatively complex drug delivery systems, requiring a substantially greater commitment of time, effort, and resource for development. Therefore, whether there is a need for solid dispersion and whether the desired bioavailability enhancement will not be achieved by other relatively less complex techniques such as particle size reduction or salt formation, should be assessed by careful in-vitro assessment of the NCE's biopharmaceutical properties and the relevance of these finding to the projected in-vitro formulation performance. Horter and dressman defined a poorly water soluble drug as one for which the dissolution time of a single dose in the GI fluids exceed the normal transit time through the absorptive regions of the GIT. Hence the absorption of poorly water soluble compounds is dose dependent and controlled by the dissolution rate in the GIT and solubility in GI fluids. The fraction of the dose absorbed will decrease with an increase in the dose size if the drug particle size or surface area is held constant, while, on the other hand, if the dose size held constant, the fraction of the dose absorbed will increase with a reduction in particle size or an increase in the particle surface area. If it is determined that complete absorption of the dose might be obtained by reducing the particle size, for instance, to approximately 2-5 µm (with in the range of standard manufacturing capability), a conventional tablet or capsule dosage form may still be feasible. However, if it is determine that particle size reduction to the sub micron range is necessary; a solid dispersion may provide a viable alternative. In silico absorption modeling with software packages, such as Gastro plus® (Simulations plus Lancaster California), have demonstrated utility determining the impact of particle size reduction on drug absorption. Effervescent granules are uncoated granules generally containing acid substances and carbonates or hydrogen carbonates which react rapidly in the presence of water to release carbon dioxide. They are intended to be dissolved or dispersed in water before administration. Effervescent granules are popular delivery systems for many pharmaceutical products such as antacids, analgesics, and cough/cold formulations. They are fast dissolving, highly soluble, stable, convenient dosage forms. The granules are added into a glass of water just before administration and the drug solution or dispersion is to be drunk immediately. The granules are quickly dispersed by internal liberation of carbon dioxide in water due to introduction between acid with alkali metal carbonates or bicarbonates in the presence of water. Due to liberation in carbon dioxide gas, the dissolution of the API in water as well as taste masking effect is enhanced. The advantages of effervescent granules compared with other dosage forms includes an opportunity for the formulator to improve taste, a more gentle action on the patient's stomach and marketing aspects. Many patients find it difficult to swallow tablets and hard gelatin capsules and thus do not comply with prescription, which results in high incidence of non-compliance on ineffective therapy granules show better flow ability, more stability, more wetting, and more uniformity in particle size (1-6).

The main objective of this project is to improve the dissolution rate of efz by improving the solubility in dissolution medium by using solid dispersion technique and to formulate effervescent granules.

MATERIALS AND METHODS

Preparation of solid dispersions of efavirenz

Solvent evaporation method (7-10)

Solid dispersion is one of the most commonly used techniques to improve the solubility of water insoluble drug which in term improves the bioavailability. Efavirenz solid dispersions were prepared by using carriers(i.e. starch and 2%SLS media) in proportions viz. 1:5, 1:10 and 1.15 (drug: carrier) by solvent evaporation method (Table-1). Methanol was added to

the mixture of drug and carrier and triturated in dry mortar until the solvent evaporated and a clear film of drug and carrier was obtained. The resultant solid dispersion was scraped out with a spatula. Dispersion was pulverized in a motor and pestle and passed through a sieve no 40. Then the prepared formulations were stored in desiccators until further use

Table-1 Composition of efavirenz physical mixtures & solid dispersions

S.no	formulation	composition	Drug:polymer
1	**PMS1**	**Efavirenz+starch**	**1:5**
2	**PMS2**	**Efavirenz+starch**	**1:10**
3	**PMS4**	**Efavirenz+starch**	**1:15**
4	**PMP1**	**Efavirenz+PVPK$_{30}$**	**1:5**
5	**PMP2**	**Efavirenz+PVPK$_{30}$**	**1:10**
6	**PMP4**	**Efavirenz+PVPK$_{30}$**	**1:15**
7	**SDS1**	**Efavirenz+starch**	**1:5**
8	**SDS2**	**Efavirenz+starch**	**1:10**
9	**SDS4**	**Efavirenz+starch**	**1:15**
10	**SDP1**	**Efavirenz+PVPK$_{30}$**	**1:5**
11	**SDP2**	**Efavirenz+PVPK$_{30}$**	**1:10**
12	**SDP4**	**Efavirenz+PVPK$_{30}$**	**1:15**

Solubility studies of efavirenz solid dispersion

Solubility measurements of efavirenz were performed according to a published method. Solid dispersions equivalent to 100 mg of efavirenz was shaken with 10ml distilled water in stoppered conical flask in an orbital shaker for 24 hours at room temperature. Subsequently, the solutions were filtered through a whatman filter paper no 1. Filtered solution was diluted properly with 2% SLS media. The diluted solutions were analyzed for the efavirenz at 247nm.

Drug content

Solid dispersions equivalent to 10 mg of efavirenz were weighed accurately and dissolved in the 10 ml of methanol. The solution was filtered, diluted suitably and drug content was analyzed at 247 nm by UV Spectrophotometer. The actual drug content was calculated using the following equation: %drug content = (actual amount of drug in solid dispersion/theoretical amount of drug in solid dispersion) × 100

***In Vitro* dissolution studies**

Dissolution studies were performed to compare the drug release from the solid dispersion, physical mixture to that of pure drug. The dissolution test was carried out for a period of 5min in pH 2% SLS media buffer. Sample of 50 mg pure drug efavirenz, physical mixture and solid dispersion equivalent to 50 mg of drug(efavirenz) were weighed and added to the dissolution medium. All the experiments were carried out it was clear that solid dispersion showed enhanced dissoluation rate compared to physical mixture and pure drug. The order of release is solid dispersion >physical mixture>pure drug. As concentration of carrier increases dissolution rate of efavirenz has also increased. Solid dispersions increased the solubility by maximizing the surface area of the drug that comes in contact with the dissolution medium. This might be due to the surface tension lowering effect of polymer to the medium, resulting in the wetting of hydrophobic drug of crystalline surface, which can be attributed to the reduction of crystallinity of drug, and therefore improved release profile.

RESULTS AND DISCUSSION

Saturation solubility analysis was carried out for pure drug, prepared physical mixtures and solid dispersion. From the results of saturation solubility studies it was observed that there was increase in solubility of drug in solid dispersions compared to physical mixtures with increase in the concentration of carrier solubility of drug increased and the solid dispersions containing $PVPK_{30}$ in the ratio of (drug to carrier) had increased the solubility almost 5 fold compared to that of pure drug (Table-2).

Table-2 Drug Content of Formulation

S.NO	FORMULATION	(%)DRUG CONTENT	(%)MOISTURE CONTENT	EFFERVISCENT TIME(MIN)
1	PMS5	98.9 ± 0.01	0.01± 0.01	1.10
2	PMS10	98.4 ± 0.01	0.01± 0.01	1.20
3	PMS15	99.2 ± 0.01	0.02± 0.01	1.30
4	SDS5	98.1 ± 0.01	0.01± 0.01	1.20
5	SDS10	99.96 ± 0.02	0.03± 0.01	1.40
6	SDS15	96.9 ± 0.01	0.01± 0.01	1.20
7	PMP5	96.4± 0.01	0.06± 0.01	2.00
8	PMP10	95.9± 0.01	0.07± 0.01	2.00
9	PMP15	97.9± 0.01	0.08± 0.01	2.10
10	SDP5	97.5± 0.01	0.04± 0.02	1.50
11	SDP10	97.5± 0.01	0.04± 0.01	1.55
12	SDP15	97.9± 0.01	0.04± 0.01	1.55

Flowability of efavirenz (pure drug) and its solid dispersions was assessed by determination of carr's index(CI), hausner's ratio(HR) and angle of repose. Micromeritic behaviors of the untreated efavirenz powder and all prepared solid dispersion. The results shows that the flowability represented in terms of carr's index, hausner'sratio and angle of repose was much improved compared to those of original powders (untreated efavirenz). In case of pure efavirenz , powder could not pass through the funnel during the angle of repose experiment. The poor flow of efavirenz could be due to the irregular shape and high fineness of the powder, which posed hurdles in the uniform flow from the funnel. These results are significantly different from those of untreated efavirenz (Table-3).

Table-3 Flow Properties of Efavirenz and its Physical Mixtures and Solid Dispersion

SAMPLE	CARR'S INDEX	HAUSNER'S RATIO	ANGLE OF REPOSE(^{0})
Pure drug	35.12	1.54	40.02
PMS5	18.34	1.22	30.77
PMS10	16.66	1.2	32.54
PMS15	9.91	1.11	36.91
PMP5	12.59	1.14	30.82
PMP10	14.53	1.17	32.25
PMP15	13.63	1.15	37.13
SDS5	14.46	1.16	32.25
SDS10	16.83	1.20	38.01
SDS15	9.64	1.10	29.0
SDP5	15.18	1.17	30.82
SDP10	9.75	1.10	34.59
SDP15	10.27	1.11	36.06

In vitro drug release studies were performed employing USP type II dissolution apparatus. The dissolution test was performed using 900 ml of 2% SLS media up to 4 min at 37^0C ± 0.5^0C and 50 rpm from the results of the dissolution studies it was observed that there was significant increase in the dissolution rate of solid dispersions compared to that of physical mixtures and pure drug and also there was increase in the dissolution rate with increased carrier content. The formulation (SDS15) containing drug: starch in the ratio of 1:15 has shown higher dissolution rate compared to other formulations with drug release of 99.96% in 3.30 min (Fig-1 and 2).

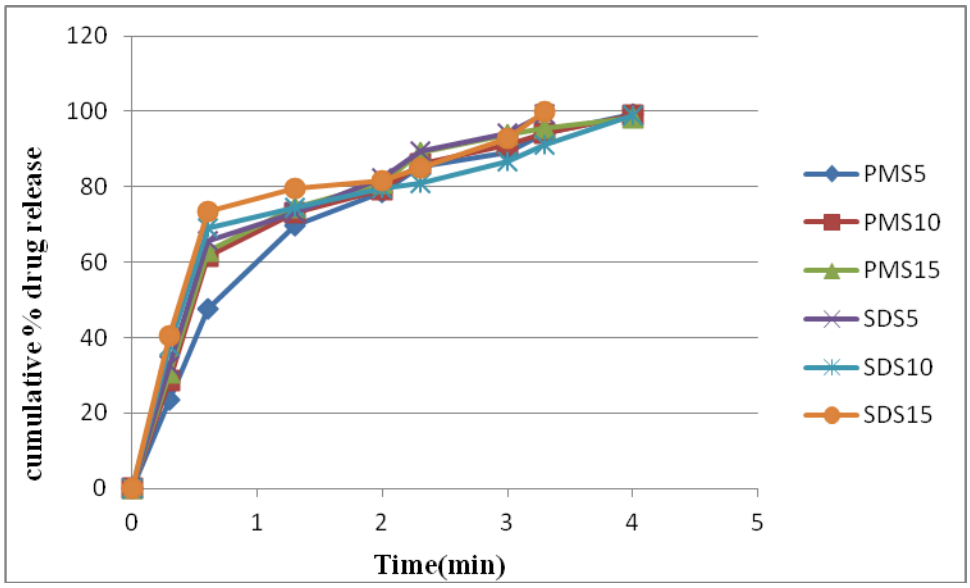

Fig-1 Comparison of dissolution profiles of pure drug,physical mixture and solid dispersion of starch and pure drug.

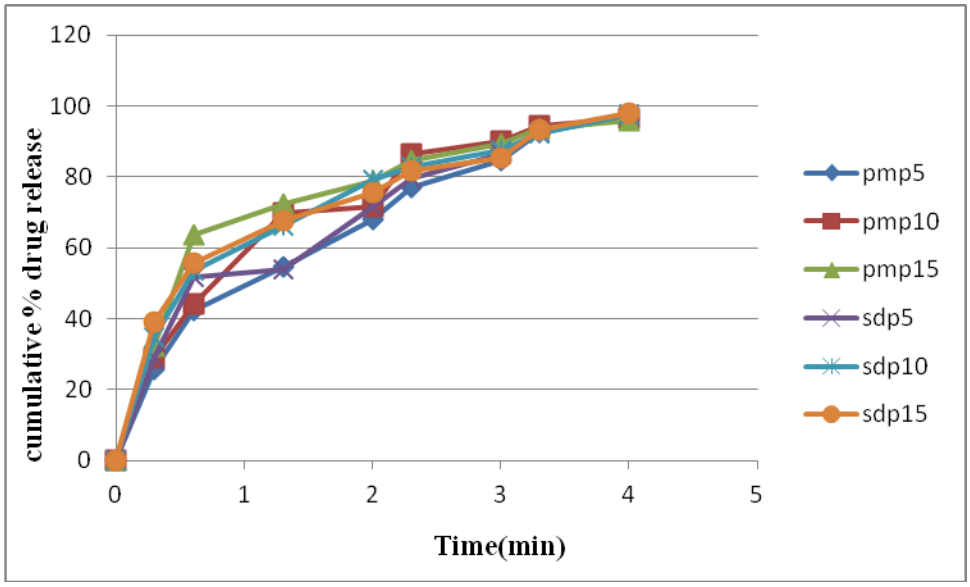

Fig-2 Comparison of dissolution profiles of pure drug, physical mixture and solid dispersion of PVP K30 and pure drug

CONCLUSION

Therapeutic effectiveness of a drug depends upon the bioavailability and ultimately upon the solubility of drug molecules. Solubility behavior of a drug is one of the key determinants of its oral bioavailability. In recent years, a no of poorly soluble drug candidates have increased tremendously. The formulation of poorly soluble drugs for oral delivery presents a challenge to the formulation scientists. The rate and extent of dissolution of the active ingredient from any dosage form often determines the rate and extent of absorption of the drug. Therefore, a drug with aqueous solubility will typically exhibit dissolution rate limited absorption. There are various techniques available to improve the solubility of poorly soluble drugs, such as micronization, nanosuspension, modification of the crystal habits, eutectic mixtures, solid dispersions, micro emulsion, self micro emulsifying drug delivery systems, cyclodextrin inclusion and lipid based delivery systems etc. Solid dispersion is one of the most promising approaches for solubility enhancement. Solid dispersion technology's are particularly promising for improving the oral absorption and bioavailability of BCS class II drugs. The drug selected for the study was Efavirenz which is used in treatment of AIDS and belongs to BCS class II drug with poor aqueous solubility. Therefore the present study was planned to improve solubility and dissolution rate of Efavirenz through solid dispersion technique. Solid dispersions of Efavirenz were prepared using $PVPK_{30}$, starch as carrier in different drug :carrier ratio 1:5, 1:10, 1:15 by employing solvent evaporation method. The prepared solid dispersion was evaluated for % drug content and saturation solubility studies. From the results of saturation solubility studies it was observed that there was decrease in solubility of drug as carrier concentration increase in physical mixtures containing starch but when compared with solid dispersion. The solubility increase 3 folds to that pure drug with carrier concentration increases. While in case of PVPK30 in physical mixtures and solid dispersions as concentration increases, solubility also increases 3 folds to that of pure drug. These solid dispersion were used for preparation of effervescent granules by using citric acid, tartaric acid and sodiumbi carbonate. These granules were evaluated for various physicochemical properties i.e., bulk density, tapped density, hausner's ratio, car's index,and angle of repose. The results were found to be within the prescribed limits indicating good flow property of granules. The prepared granules were also evaluated for % moisture content, %drug content and effervescence time and from the results the drug content was found to be in the range content among various formulations. The moisture content was found to be within the range of a minimum of 0.01 ±0.01 and maximum of 0.08 ±0.01 indicates the ability, free flow ability. The effervescence time was less then 2.10 sec among all formulations PMS15 showed the least effervescence time (1.10 sec) due to its less moisture content. The formulation PMP 15 showed more effervescence time compared to others. In vitro drug release studies were performed employing USP type II dissolution apparatus. The dissolution test was performed using 900 ml of 2% SLS media upto 4 min at $37^0C \pm 0.5^0C$ and 50 rpm from the results of the dissolution studies it was observed that there was significant increase in the dissolution rate of solid dispersions compared to that of physical mixtures and pure drug and also there was increase in the dissolution rate with increased carrier content. The formulation (SDS15) containing drug : starch in the ratio of 1:15 has shown higher dissolution rate compared to other formulations with drug release of 99. The present study aimed at improving the aqueous solubility of poorly soluble drug Efavirenz by effervescent granulation of solid dispersion technique. From the results of the present study it can be concluded that the solubility of the drug can be significantly enhanced with the natural polymer as that of the synthetic polymer when compared to that of pure drug the order of increase in solubility is SDS 15> SDP15> PMS5> SDP10> PMP15> PMP10> SDS110> PMP5> SDS5> PMS10> PMS15. The order of increase in dissolution rate was found to be SDS15> SDS5> PMS5> PMS10> SDS10> PMS15> SDP15> SDP5> SDP10-> PMP5> PMP10> PMP15.

Formulation containing 1:15 ratio of drug:starch is considered as best formulation as it has shown highest drug release in short time i.e., 99.96% in 3.30 min. therefore starch can be successfully employed for developing effervescent granules of poolrly soluble drugs like efavirenz with solid dispersion technique.

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