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Original Article

FORMULATION AND EVALUATION OF SOLID DISPERSION CONTAINING ASPIRIN

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ABSTRACT

Objective: The objective of the study is to increase the solubility by solid dispersion method and to compare dissolution of pure drug and solid dispersions.Aspirin (Acetyl Salicylic Acid)is poorly soluble in water show dissolution limited absorption and causes gastrointestinal (GI) irritation. Solubility enhancement of poorly aqueous soluble drugs is an important aspect of formulation development. **Methods:** The present study is an attempt to enhance the solubility of aspirin by fusion (Melt) method using aspirin and polyethylene glycol 6000 as a carrier in the ratio of 1:1, 1:2, 1:3 and 1:4. The complex of aspirin with polyethylene glycol6000 shows enhanced solubility than the pure drug and the complex can also reduce the gastrointestinal irritation.Micromeritic properties of granules were evaluated as well as dissolution rate studies were performed in phosphate buffer pH6.8.**Results:** Micromeritic properties of granules were found in specified limits. The dissolution ratewas found tobe 95.94 1.17% for optimized formulation F4 at the end of 90 mins. **Conclusion:** It is concluded that dissolution of the aspirin could be improved by the solid dispersion and PEG6000 based solid dispersions were more effective in enhancing the dissolution.

Keywords: Aspirin, Solid dispersion, PEG 6000, fusion method.

INTRODUCTION

Aspirin (acetylsalicylic acid, AS) is widely used therapeutic substances due to its analgesic, antipyretic and anti-inflammatory properties, despite the proliferation in development of new non-steroidal anti-inflammatory drugs (NSAIDs). As is used as the most effective over-the-counter drugs in the treatment of rheumatic diseases. The low dose of AS is given for the prevention and treatment of cardiovascular diseases, strokes, and disorders associated with platelet aggregability [1] due to its anti-thrombotic properties.AS inhibits prostaglandin synthesis and COX-II inhibitor.Mortality of human cancers, especially colon cancer [2] is reduced by the use of AS.The oral administration of AS requires high and frequent dosing because it undergoes extensive pre-systemic metabolism. The long term and chronic oral aspirin are associated with serious gastrointestinal side-effects. Hence solubility and bioavailability enhancement of AS is essential to reduce the gastrointestinal side-effects [3].

Water-soluble pharmaceutical carriers [4] can be used in the pharmaceutical field to enhance aqueous solubility, dissolution rate and bioavailability of many poorly water soluble drugs.Polyethylene glycols (PEGs) with molecular weights of 1,500–20,000 are widely used as water-soluble carriers for preparation of solid dispersions of many poorly water soluble drugs. The carriers exhibit low melting point, rapid solidification rate, low toxicity, low costs and good solubility in water and most of the organic solvents [5, 6].PEG can solubilize many of poorly water soluble drugs.The drugs with low aqueous solubility and high membrane permeability are categorized as Class II drugs according to biopharmaceutical classification system (BCS).Hence solid dispersion technologies are used to improve the oral absorption and bioavailability of BCS Class II drugs. By the method of solid dispersion, preparation drug disperses in the matrix a hydrophilic matrix and a hydrophobic drug, thereby resulting in a solid dispersion. When the solid dispersion is exposed to aqueous media, the carrier dissolves and the drug releases as fine colloidal particles. The resulting enhanced surface area produces higher dissolution rate and bioavailability of poorly water-soluble [7] drugs. A present study aimed to compare solubility of aspirin alone, complexes of aspirin with PEG 6000 using solid dispersion technique.

MATERIALS AND METHODS

Materials

Aspirin was obtained from Research-lab fine chem. Industries India. PEG 6000 was purchased from S D fine-chem limited India. Methanol from SD fine-chem limited was used. All reagents were of A.R. grade. Double distilled water was used throughout the experiment.

Methods

Preparation of solid dispersion

Solid dispersions (SD) were prepared by melting the accurately weighed amounts of PEG 6000 in a water bath, and the drug was dispersed in the molten solution. The mixtures were repeatedly stirred after 10 min cooled at room temperature. Solid mass obtained was passed through the sieve # 40 and stored in a vacuum desiccator until use. The required drug to carrier ratio for formulations was shown in table 1.

Table 1: **Formulation of solid dispersion of aspirin containing carrier PEG6000**

Batch	Drug: carrier	Quantity of drug(mg)	Quantity of carrier(mg)
F1	1:1	500	500
F2	1:2	500	1000
F3	1:3	500	1500
F4	1:4	500	2000

Characterization of solid dispersions

Micromeritic characterization [8]

Angle of repose (θ)

Funnel method is used to determine the angle of repose. The accurately weighed powder blend was taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the powder blend. The blends were allowed to flow freely onto the surface. The diameter of the powder cone was measured. Angle of repose is calculated using the following equation

$\tan \theta = h/r$ ……..…….……..……..…….. (1)

$\theta = \tan^{-1}(h/r)$ ..... (2)

Where θ is the angle of repose, h is the height of heap in cm and r is the radius of the circular support (cone) in cm.

Bulk density (e_b)

Bulk density is determined by pouring the granules into a graduated cylinder of bulk density apparatus (Sisco, India). The bulk volume (V_b) and mass (m) of the granules are determined. The bulk density is calculated by using the following formula.

$e_b = m/V_b$ ..... (3)

Tapped density (e_t)

The measuring cylinder containing a known mass of granules blend is tapped 1000 times for a fixed time in bulk density apparatus (Sisco, India). The minimum volume occupied in the cylinder (V_t) and mass of the granules (m) are measured. The tapped density is measured by using the following formula.

$e_t = m/V_t$ ..... (4)

Compressibility index (Carr's index):

The compressibility index determines the flow property characteristics of granules developed by Carr. The percentage compressibility of granules is a direct measure of the potential powder arch and stability. The Carr's index can be calculated by the following formula.

$$\%\text{Carr's index (C.I)} = \frac{e_t - e_b}{e_t} \times 100 \quad \text{..... (5)}$$

Where e_t is the tapped density of granules and e_b is bulk density of granules

Hausner's ratio

Hausner's ratio is used for the determination of flow properties of granules. The ratio can be calculated by the taking the ratio of tapped density to the ratio of bulk density.

Mathematically

$$\text{Hausner's ratio (H.R)} = \frac{et}{eb} \quad \text{.....(6)}$$

Physical characterization [9, 10]

Solubility studies

The saturation solubility of pure Aspirin, physical mixtures and solid dispersions were determined and compared with each other. The known excess samples (Aspirin solid dispersions, and pure Aspirin) were added to 5 ml of pH 6.8 phosphate buffer and these samples were rotated in a water bath (37 ± 0.5°C) for 48 hours. The samples were then filtered through 0.45 µm membrane filter, suitably diluted, and analyzed by UV-VIS spectrophotomer (Shimadzu Corporation, Japan) at 265 nm wavelength.

Drug content

The drug content in each solid dispersions and the physical mixture was determined by the UV spectroscopic method. An accurately weighed quantity of solid dispersion or physical mixture, equivalent to 100 mg of Aspirin, was transferred to a 100 mL volumetric flask containing 5 mL of methanol and dissolved. The volume was made up to 100 mL with pH 6.8. The solution was filtered, and the absorbance was measured after suitable dilutions by using UV-VIS spectrophotometer (Shimadzu Corporation, Japan) at 265 nm wavelengths.

Percentage Yield

To determine the efficiency of solid dispersion production percentage yield was calculated. In this method preweighedsoliddispersions were collected to determine practical yield. The percentage yield can be calculated using the given equation 3.

$$\%\text{ Yield} = \frac{\text{Practical Yield}}{\text{Theoretical yield}} \times 100 \quad \text{..... (7)}$$

***In vitro* dissolution study**

Dissolution studies were performed in pH 6.8 phosphate buffer containing 900ml at 37 ± 0.5°C, using USP type-II apparatus with paddle rotating at 75 rpm. Sample of pure Aspirin, solid dispersions as well as physical mixtures, each containing 500 mg equivalent of aspirin were subjected to dissolution. Aliquots of 5 ml were withdrawn at time intervals of 10, 20, 30, 40, 50, 60, 70, 80, and 90 min were filtered and spectrophotometrically analyzed at 265 nm. The same amount of withdrawn volume was replaced with the dissolution medium in order to maintain the sink condition.

Accelerated stability study

Stability study [11] was conducted on optimized formulation. The formulations were packed in an air tight container and stored in stability chamber at 40 ± 2°C and 75 ± 5% RH for a period of 3 months. The samples were then withdrawn at interval of 30, 60 and 90 days and were evaluated for drug content and In-vitro dissolution studies.

RESULTS AND DISCUSSION

Micromeritic characterization of SD formulations:

All thegranules were evaluated for micromeritic properties (Table-2) such as angle of repose bulk density, tapped density, Carr's index and Hausner's ratio. All were found to be acceptable limits.

Physical characterization

All the granules were evaluated for physical characterizationsuch as solubility,drug content, and %yield. It is shown in table 3.

Table 2: Micromeritic characterization of SD granules

Formulation code	Angle of repose (degree)[a] ± S.D	Bulk density (gm/ml)[a] ± S.D	Tapped density (gm/ml)[a] ± S.D	Carr's Index (%)[a] ± S.D	Hausner's Ratio[a] ± S.D
F1	28.78±0.14	0.528±0.12	0.562±0.11	6.05±0.14	1.06±0.09
F2	27.82±0.12	0.524±0.14	0.567±0.12	7.58±0.12	1.08±0.11
F3	26.19±0.11	0.525±0.11	0.571±0.12	8.05±0.14	1.08±0.09
F4	25.01±0.12	0.526±0.04	0.558±0.06	5.73±0.05	1.06±0.03

N.B.All values are expressed as mean± S.D, [a]n = 3

.**Table 3: Physical evaluation**

Formulation code	Solubility(mg/ml)	Drug content	%Yield
Pure drug	13.85±0.79	----	----
F1	20.96±0.93	98.42±1.09	78.73±1.43
F2	29.85±1.09	99.02±1.11	85.46±1.55
F3	33.44±0.77	99.06±1.02	91.96±1.67
F4	35.97±0.62	99.87±1.15	97.98±1.08

***In Vitro* dissolution study**

The *in vitro* drug release was carried out in phosphate buffer of pH 6.8. The % *in vitro* drug release from formulations pure drug, F1, F2, F3 and F4 at the end of 90 mins was found to be16.27±1.14,70.35±1.12,86.05±1.34,90.43±1.19, and 95.94±1.17 % respectively. The optimized formulation profile was given by F4 contained 1:4 as a drug: carrier ratio.

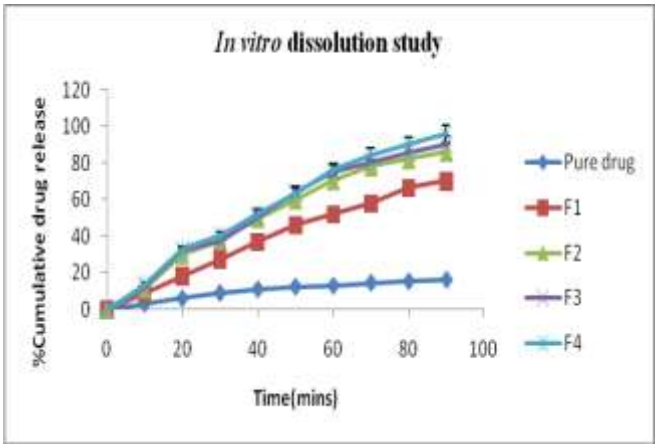

Fig. 1: *In vitro* release profiles showing aspirin release from various fabricated formulations F1-F4 and pure drug.

Stability studies

From short term stability studies of optimized formulation F4, it was confirmed that there were no significance changes in drug content and % drug release. Hence it was concluded the formulation was stable in a storage condition.

CONCLUSION

The solubility and dissolution studies showed there is a possibility of improved solubility of aspirin through solid dispersion with PEG 6000 by fusion method. A maximum increase in dissolution rate was obtained with aspirin in F4. Finally, it is concluded that solid dispersion of aspirin using hydrophilic polymers improved the solubility, dissolution rate and thereby enhancing its systemic availability.

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