Research Article

Formulation and Evaluation of Solid Dispersion Containing Paracetamol

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ABSTRACT

Paracetamol is sparingly soluble and bitter in taste and widely used as an analgesic and antipyretic. Solid dispersion of drug with different polymers was attempted to improve solubility of paracetamol. The aim of this study was to prepare, characterize and compare solid dispersions of paracetamol, with polyethylene glycol 6000 as carrier. The solid dispersions were prepared by fusion method. The formulations were evaluated for percent yield, drug content, micromeritics and *in vitro* dissolution studies. In this study it was indicated that there occurred an increase in drug release for solid dispersion as compared to the pure drug taken alone. Based on the drug release pattern, F4 formulation showed more drug release as compared to other developed formulations. Finally, solid dispersion containing PEG 6000, as a carrier, gave faster dissolution rates among all the formulations and was selected as the best formulation in this study

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

INTRODUCTION

Pharmaceutical carriers like water-soluble carriers are used in the pharmaceutical field because of their ability to enhance aqueous solubility, dissolution rate and bioavailbility of many poorly water soluble drugs. Polyethylene glycols (PEGs) with molecular weights of 1,500–20,000 are mostly used as water-soluble carriers[1] for preparation of solid dispersions of many poorly water soluble drugs. The carriers have low melting point, rapid solidification rate, low toxicity, low costs and good solubility in water and most of organic solvents. It has high ability to solubilize many of poorly water soluble drugs[2-4]. In the biopharmaceutical classification system (BCS) drugs with low aqueous solubility and high membrane permeability are categorized as Class II drugs. Therefore, solid dispersion technologies are particularly promising for improving the oral absorption and bioavailability of BCS Class II drugs. In case of solid dispersion drug disperse in the matrix generally a hydrophilic matrix and a hydrophobic drug, thereby forming 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[5] and bioavailability of poorly water-soluble drugs.

Paracetamol[6] (Acetaminophen) is a medication used to treat pain and fever. It is typically used for mild to moderate pain. It is often sold in combination with other ingredients such as in

many cold medications. In combination with opoid pain medication, paracetamol is also used for more severe pain such as cancer pain and after surgery. It is typically used either by mouth or rectally but is also available intravenously. Effects last between 2 and 4 hours. Paracetamol is generally safe at recommended doses. Serious skin rashes may rarely occur, and too high a dose can result in liver failure. It appears to be safe during pregnancy and when breastfeeding. In those with liver disease, it may still be used, but in lower doses. Paracetamol is classified as a mild analgesic. The aim of a present study was to compare solubility of paracetamol alone, complexes of paracetamol with PEG 6000 using solid dispersion technique.

MATERIALS AND METHODS

Materials

Paracetamol was obtained from Cipla Pvt Ltd.,Goa. India. PEG 6000 was purchased from S D fine-chem limited India. 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 stirred repeatedly, after 10 min cooled at room temperature. Solid mass obtained was passed through the sieve # 40 and stored in vacuum desiccator until use. The required drug to carrier ratio for formulations was shown in table 1.

Characterization of solid dispersions

Micromeritic characterization[7,8]

Angle of repose

The angle of repose of granules blend was determined by the fixed funnel method. The accurately weighed quantity of granules was taken in a funnel. The height of funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the granules. The granules are allowed to flow through the funnel freely onto the surface. The diameter of powder cone was measured and angle of repose was calculated using the following equation

$$\tan\Theta = h/r$$

$$\Theta = \tan^{-1}(h/r)$$

Where Θ is the angle of repose, h is the height of cone in cm and r is the radius of the cone base in cm.

Bulk density (e_b)

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

Bulk density (e_b)=Mass of granules(m)/Bulk volume of granules(V_b)

Tapped density (e_t)

The measuring cylinder containing known mass (m)of granules blend was 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) was measured. The tapped density was measured by using the following formula.

Tapped density (e_t)= Mass of granules(m)/Tapped volume of granules(V_t)

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.

$$\%\text{Carr's index (C.I)} = \frac{et - eb}{et} \times 100 \quad \text{.....(1)}$$

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.

Matematically

$$\text{Hausner's ratio(H.R)} = \frac{et}{eb} \quad \text{..... (2)}$$

Physical characterization

Solubility studies

The saturation solubility of pure Paracetamol, physical mixtures and solid dispersions were determined and compared with each other. The known excess samples (Paracetamol solid dispersions, and pure Paracetamol) 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 257 nm wavelength.

Drug content

The drug content in each solid dispersions and physical mixture was determined by the UV spectroscopic method. An accurately weighed quantity of solid dispersion or physical mixture, equivalent to 100 mg of Paracetamol, 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 spectrophotomer (Shimadzu Corporation, Japan) at 257 nm wavelength.

Percentage Yield

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

$$\% \text{ Yield} = \frac{\text{Practical yield}}{\text{Theoretical yield}} \times 100 \quad \text{.....(3)}$$

***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 Paracetamol, solid dispersions as well as physical mixtures, each containing 500 mg equivalent of paracetamol were subjected to dissolution. Aliquots of 5 ml were withdrawn at time intervals of 10, 20, 30, 40,50, and 60 min were filtered and spectrophotometrically analyzed at 257 nm. The same amount of withdrawn volume was replaced with the dissolution medium in order to maintain the sink condition.

Accelerated stability study[9]

Stability study 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 the granules 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 characterization such as solubility, drug content, and %yield. It is shown in table 3.

***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 60 mins was found to be 51.72±1.14, 77.41±1.16, 83.98±1.35,88.23± 1.19,and 97.44±1.12 % respectively. The opti-mized formulation profile was given by F4 contained 1:4 as drug: carrier ratio (Fig. 1).

Table 1: Formulation of solid dispersion of paracetamol 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

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	26.32±0.07	0.514±0.06	0.559±0.08	8.05±0.06	1.08±0.08
F2	25.20±0.06	0.517±0.08	0.566±0.12	8.65±0.11	1.09±0.06
F3	25.31±0.12	0.526±0.04	0.558±0.06	5.73±0.05	1.06±0.03
F4	24.11±0.07	0.521±0.12	0.554±0.14	5.95±0.08	1.06±0.08

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

Table 3: Physical evaluation

Formulation code	Solubility (mg/ml)[a]	Drug content(%)[a]	Yield(%)[a]
Pure drug	0.084±0.79	----	----
F1	0.148±0.93	97.11±1.09	77.73±1.43
F2	0.173±1.09	99.31±1.11	83.46±1.55
F3	0.195±0.77	99.57±1.02	90.96±1.67
F4	0.203±0.62	99.88±1.15	96.98±1.08

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

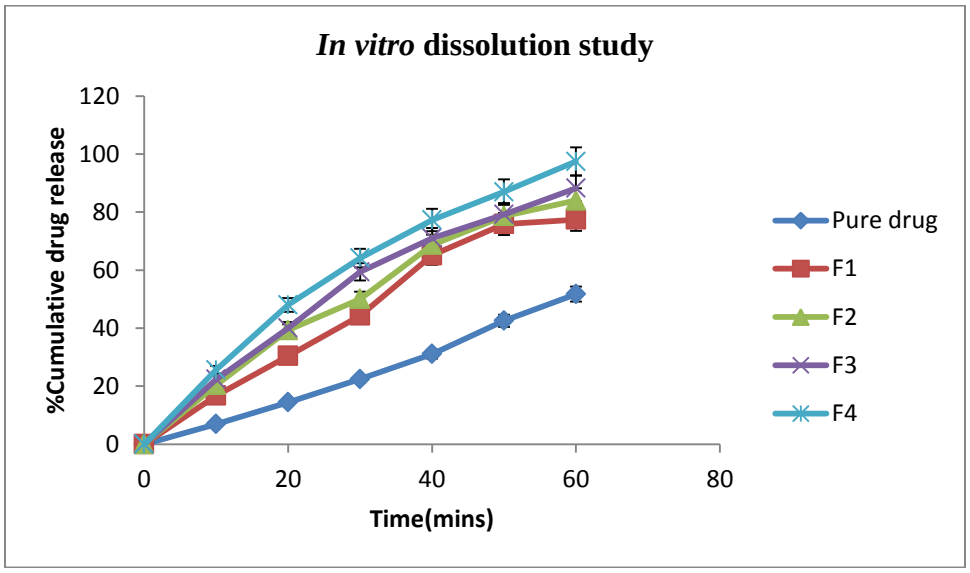

Fig. 1: *In vitro* release profiles showing paracetamol release from various fabricated formulations F1-F4 and pure drug (n=3)

Stability studies

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

CONCLUSION

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

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