Research Article
ISSN: 0974-6943

D. Akiladevi et al. / Journal of Pharmacy Research 2010, 3(12),2846-2849

Available online through
www.jpronline.info

Dissolution enhancement of Paracetamol by solid dispersion technique

D. Akiladevi *[1], Sachinandan Basak[2]

[1] Department of Pharmaceutical Sciences, Mohamed Sathak A.J College of Pharmacy, Sholinganallur, Chennai-600119,

[2]Dr.Reddy's Laboratories Ltd, Bachupalli, Qutubullapur, RR district 500090, Andhrapradesh.

Received on: 12-08-2010; Revised on: 06-10-2010; Accepted on:08-11-2010

ABSTRACT

Paracetamol is a potent anti-inflammatory analgesic agent indicated for acute and chronic treatment of rheumatoid arthritis, osteoarthritis, and ankylosing spondylytis. Paracetamol is poorly water soluble and may show dissolution limited absorption. The solid dispersion of paracetamol by physical triturating method, and fusion method were prepared using 1:1,1:4 and 1:5 ratios of drug and polymers (PEG 4000, PEG 6000 and urea). The solid dispersion (SD) was characterized for physical appearance, solubility, IR, and *in vitro* dissolution studies. FTIR study revealed that drug was stable in SDs. Solubility of paracetamol from SDs increased in distilled water. The drug content was found to be high and uniformly distributed in the all formulation. The *in vitro* dissolution studies were carried using USP type XXVII (paddle) type dissolution apparatus. The prepared dispersion showed marked increase in the dissolution rate of paracetamol than that of pure drug. The dispersion with PEG 6000 (1:5) by fusion method showed faster dissolution rate (107.26%) as compared to other dispersions with PEG 4000 and urea (1:4 and 1:5) whichever prepared by physical mixture (PM) and fusion method). Of the three carriers used, dissolution of the drug was more in PEG 6000 based SDs. It is concluded that dissolution of the Paracetamol could be improved by the solid dispersion and PEG6000 based solid dispersions were more effective in enhancing the dissolution.

Keywords: Paracetamol, solid dispersion**,** PEG 4000, PEG 6000, Urea, *in vitro* release

INTRODUCTION

The enhancement of oral bioavailability of poorly water soluble drugs remains one of the most challenging aspects of drug development[1]. Together with the permeability, the solubility behavior of a drug is a key determinant of its oral bioavailability. There have always been certain drugs for which solubility has presented a challenge to the development of a suitable formulation for oral administration. The formulation of poorly soluble compounds for oral delivery at present is one of the most frequent and greatest challenges to formulation scientists in the pharmaceutical industry. However, the most attractive option for increasing the release rate is improvement of the solubility through formulation approaches. Although salt formation, solubilization and particle size reduction have commonly been used to increase dissolution rate and thereby oral absorption and bioavailability of low water soluble drugs [2-4] there are practical limitation of these techniques. In 1961, Sekiguchi and Obi [5] developed a practical method whereby many of the limitations with the bioavailability enhancement of poorly water-soluble drugs can be overcome. This method, which was later, termed solid dispersion which involved the formation of eutectic mixture of drugs with water-soluble carriers by the melting of their physical mixtures.

MATERIALS AND METHODS

Paracetamol was obtained from Apex Laboratories, Chennai, as a gift sample. PEG 4000, PEG 6000, Urea, Sodium hydroxide (NaOH), Potassium di-hydrogen phosphate were purchased from S.D.fine chemicals limited, Mumbai. All the carriers used were of analytical grade.

Preparation of solid dispersion [10-13]

Solid dispersions were prepared by melting the accurately weighed amounts of carriers (PEG 4000, PEG 6000 and urea) in a water bath and the drug was dispersed in the molten solution. Fusion method was used for the preparation of solid dispersions. Briefly appropriate amount of paracetamol was taken in china dish and required amount of carriers (PEG 4000, PEG 6000 and urea) were added to prepare required drug to carrier ratio for formulations as shown in table 1.Then the mixture was heated under controlled temperature to melt drug and carrier with continuous stirring. The melted preparation was transferred to porcelain tile to solidify and cooled in an ice bath. The solid dispersions prepared were pulverized and sifted (80#) and stored in a desiccator.

***Corresponding author.**
D. Akiladevi
Department of Pharmaceutical Sciences,
Mohamed Sathak A.J College of Pharmacy,
Sholinganallur,
Chennai-600119.
Tel.: 044-24502572
Telefax: +91-44-24502573
E-mail:akisaravana@yahoo.co.in

Preparation of physical mixture and drug content uniformity

Drug and carriers physical mixture were prepared by slightly grinding drug paracetamol and carriers (PEG 4000, PEG 6000 and urea)in mortar for 2 min at the required drug/carriers ratio (as shown in table 1). Then the powder was passed through the sieve no - 80. The resulted product was stored in desiccator to carry out further analysis. The drug content uniformity was estimated using solid dispersion of 100 mg equivalent of paracetamol in pH 5.8 phosphate buffer as solvent. The estimation was done in a UV/Visible spectrophotometer at 257nm.

Evaluation of Solid dispersions

Physical characterization and saturation solubility study [9]

The excess amount of the formulations (PMs and SDs) was added to conical flask containing10 ml of distilled water and subjected to shaking on a rotary shaker for 48 hours at 37°C. Then the flasks were removed and filtered. Suitable aliquots were withdrawn from the filtered solution and analyzed for the drug content after appropriate dilution with distilled water and compared with pure drug solubility.

FT-IR study of pure drug and all preparations [14]

For all the formulations and paracetamol the pellets have been prepared using potassium bromide (KBr) for FT-IR study. The pellets were subjected to FT-IR instrument 'Perkin Elmer FTIR spectrometer, spectrum 1000 Germany' for the collection of IR spectra which are illustrated in figures 4 and 5.

Drug content analysis

Preparations equivalent to 20 mg was weighed accurately and transferred to 100 ml volumetric flask and dissolved in phosphate buffer pH 5.8. The volume was made up with phosphate buffer pH 5.8 up to the mark. AAfter suitable dilution, the absorbance of the above solution was measured at 243 nm using appropriate blank solution. The drug content of paracetamol was calculated using calibration curve.

In vitro release studies [6-8]

Accurately weighed amount of sample was taken for dissolution studies. Aliquots of sample were withdrawn at predetermined intervals of time and analyzed for drug release by measuring the absorbance at 243nm using phosphate buffer pH 5.8 as dissolution medium. The volume withdrawn at each time intervals were replaced with same quantity of fresh medium.

Stability studies

Each SDs formulation was prepared in duplicate and each analysis was duplicated. Effect of formulation variables on disintegration time and release parameters $t_{50\%}$ and $t_{80\%}$) were tested for significance by using analysis of variance (ANOVA: single factor) with the aid of Microsoft® Excel 2002. Difference was considered significant when P <0.05.

Table 1. Physical characteristics and Solubility studies of solid dispersions

Formulation code	Nature of Formulation	Carrier	Drug: carrier ratio	Method	Drug solubility in water mg/ml (±SD, n=3)
Pure Drug	White crystalline powder	-	-		0.084±0.015
PM_1	Off white sticky particles	PEG4000			
			1:1	Physical mixture	0.149±0.012
SD1	Off white soft particles		1:1 Solid dispersions (Fusion method)		
			1:4		
			1:5		0.201±0.012
SD2	Solid sticky lumps				0.215±0.013
SD3	Solid sticky lumps				0.224±0.018
PM_2	Off white sticky particles	PEG6000			
			1:1	Physical mixture	0.152±0.011
SD_4	Off white soft particles		1:1 Solid dispersions (Fusion method)		
			1:4		
			1:5		0.298±0.019
SD_5	Solid sticky lumps				0.319±0.014
SD_6	Solid sticky lumps				0.339±0.017
PM_3	White free flowing powder	Urea			
			1:1	Physical mixture	0.142±0.016
SD_7	White free flowing powder		1:1 Solid dispersions (Fusion method)		
			1:4		
			1:5		0.175±0.013
SD_8	White free flowing powder				0.196±0.014
SD_9	White free flowing powder				0.202±0.014

Table 2. *In vitro* dissolution data for pure drug and solid dispersions

Time (min)	Cumulative drug release (%) ± Standard deviation												
	Puredrug	PM_1	SD_1	SD_2	SD_3	PM_2	SD_4	SD_5	SD_6	PM_3	SD_7	SD_8	SD_9
10	29.2±2.3	39.3±3.5	41.2±2.7	49.8±5.1	51.2±2.8	32.6±5.1	41.5±4.2	42.3±2.1	53.2±2.7	67.2±5.2	70.1±1.9	70.2±2.8	83.1±2.7
20	47.4±3.2	60.8±4.2	65.7±3.9	72.8±4.3	87.3±4.6	55.4±2.1	65.9±2.9	70.5±2.3	81.6±1.3	77.2±3.8	79.6±1.9	80.5±3.9	98.4±1.8
30	55.4±4.2	80.6±3.6	91.2±4.5	97.4±3.4	100±3.9	88.6±3.4	98.4±2.9	100±1.2	107.2±2.5	82.4±2.6	81.6±2.2	85.3±2.7	100.8±3.8

Fig.1: Diffusion profile of Paracetamol :PEG 4000 formulations in phosphate buffer pH 5.8

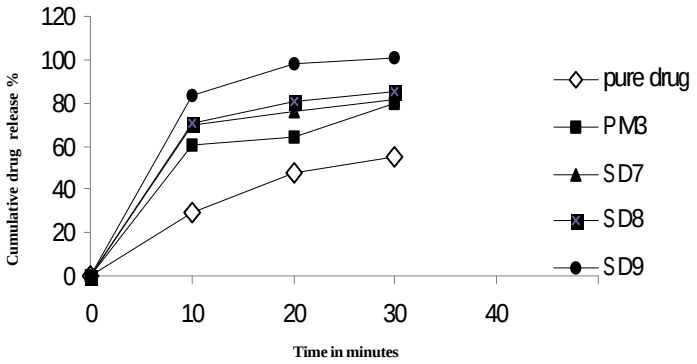

Fig.2: Diffusion profile of Paracetamol :PEG 6000 formulations in phosphate buffer pH 5.8

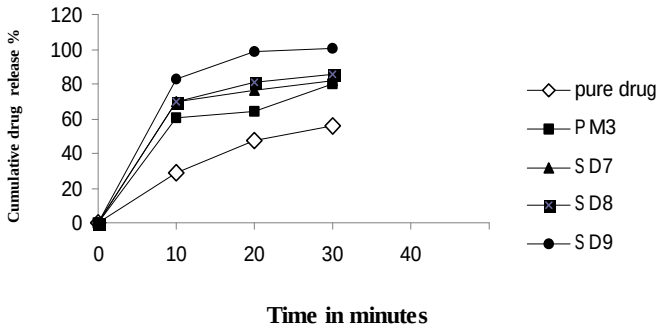

Fig.3: Diffusion profile of Paracetamol :Urea formulations in phosphate buffer pH 5.8

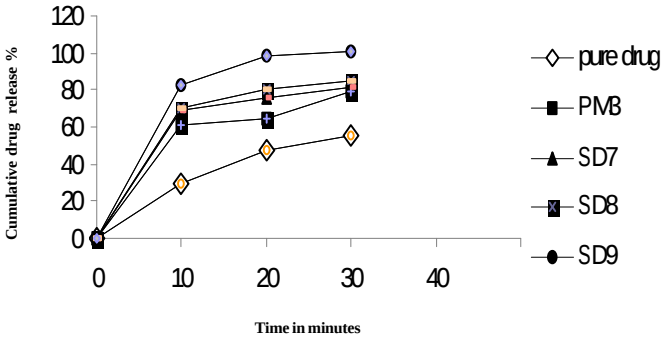

Fig-4 a) FT-IR of Paracetamol

Fig-4 b) FT-IR of PEG 4000

Fig-4 c) FT-IR of PMPEG 4000

Fig-4 d) FT-IR of SDPEG 4000

Fig-5 a) FT-IR of Paracetamol

Fig-5 b) FT-IR PEG 6000

Fig-5 c) FT-IR of PMPEG 6000

Fig-5 d) FT-IR of SDPEG 6000

RESULTS AND DISCUSSION

Physical characterization and Saturation Solubility study

Paracetamol is practically insoluble in water as the intrinsic solubility of paracetamol in pure water at room temperature is found to be 0.084mg/ml. Among PMs and SDs (1:5) the carrier PEG 6000 containing PM and SD showed highest saturation solubility. This may be due to the inherent differences between the carriers in terms of hydration, dissolution and possible complexation of drug with different carriers.

IR spectroscopy

These significant changes indicate the possibility of intermolecular hydrogen bonding between the –NH group of paracetamol and –OH group of PEG 6000. Comparison spectra of PMPEG6000 and SDPEG 6000 with drug and carrier showed significant changes. However, although little shifts in the stretching vibrationdue to –CH2 groups (of PEG 6000) appeared at two different wave numbers 2879.5cm^{-1}, and 2875.75 cm^{-1} respectively Suggesting possible difference in the degree of interaction between drug and carrier in PM and SD. A decrease in the intensity of peak of –NH group of paracetamol at 3319.3 cm^{-1}) or ternary amide peak of PEG 4000 (at 1642.3 cm^{-1}) may support intermolecular hydrogen bonding between drug and carrier in both physical mixture and solid dispersion. A decrease in the intensity of bands may also be due to the amount of compounds. Thus it can be concluded with some reservation, the absences of interaction between two compounds by FTIR.

Drug content analysis

Drug content is found to be between 95.72 % and 107.63 %. All the PMs and SDs showed presence of high drug content and low standard deviations of results. It is indicated that the drug is uniformly dispersed in the powder formulation. Therefore, the method used in this study appears to be reproducible for the preparation of SDs.

In vitro dissolution study

The formulation of solid dispersion of paracetamol with various carriers like PEG 4000, PEG 6000 and Urea were screened for the selection of suitable carriers. These carriers were found to be encouraging since they did not undergo any chemical change during the preparation of solid dispersion. The solid dispersion of paracetamol with carriers PEG 4000, PEG 6000, and Urea showed a marked increase in the dissolution rate in pH 5.8 phosphate buffer. Dissolution of the paracetamol increased with increasing proportions of carriers and $T_{50\%}$ and $T_{70\%}$ values were least with the SDs of urea (i.e.1:1-1:5). Above all the formulations the ratio of paracetamol: PEG 6000 (SD6) showed (1:5) maximum proving that higher concentration of matrix formed with PEG 6000 of ratio 1:5 increased the dissolution rate. These observations indicate the enhanced dissolution of SDs with increase in the concentration of carriers possibly due to the increased wettability of the drug by the carrier, drug particle size reduction in the course of the solid dispersion preparation, polymorphic transformation of drug crystals and chemical interactions between drug and carrier.

Stability studies

Formulations (SDPEG4000, SDPEG6000 and urea) which showed promising results were subjected to stability studies at ambient room conditions for 3 months. After 3 months, SDs did not show any change in physical appearance or drug content. It indicates that the drug was stable in SDs even after three months of short term storage. Initially solubility studies were conducted to analyze the solubility of Paracetamol in different solvents/buffers. Formulation studies included the preparation of physical mixtures (PMs) and solid dispersion (SDs) of Paracetamol with different carrier (PEG 4000, PEG 6000 and urea) with solvent method and their physico-chemical characterization using FT-IR spectroscopy, solubility studies, drug content analysis, dissolution studies and stability studies. All the PMs and SDs show high drug content (>95 %). The dissolution of paracetamol from the PMs was higher than pure drug. The formulations of paracetamol in SDs significantly improved the dissolution of paracetamol. SDs of paracetamol with the same proportion of PEG 6000 as a carrier was superior in dissolving Paracetamol compared with PEG 4000and urea. The dissolution of paracetamol from SDs of PEG6000 increased with increasing proportion of carrier from 1:1 to 1:5. Three months stability studies of selected formulations at ambient room conditions showed no change in the physical character and drug content. It is concluded that dissolution of the paracetamol could be improved by solid dispersions and PEG 6000 based solid dispersions are more effective in the enhancing the dissolution. The dissolution of a poorly/sparingly soluble drug is based on the bioavailability and method employed for the particle size reduction of different methods used for

the preparation of solid dispersion was briefly reviewed in the introduction. The spectrophotometric method was most suitable for estimation of the drug content and dissolution study of various solid dispersion of paracetamol it was adopted throughout the investigation. The formulation of solid dispersion of paracetamol with various carriers like PEG 4000, PEG 6000 and Urea were screened for the selection of suitable carriers. These carriers were found to be encouraging since they did not undergo any chemical change during the preparation of solid dispersion. Solid dispersions of paracetamol in pH 5.8 phosphate buffer were prepared using the dissolution apparatus described in the USP Paddle-II. The results obtained in the dissolution study were found to be satisfactory. This revealed that the solid dispersion of paracetamol with carriers PEG 4000, PEG 6000, and Urea showed a marked increase in the dissolution rate in pH 5.8 phosphate buffer. Above all the formulations the ratio of Parcetamol: PEG 6000 (SD4) showed (1:5) maximum proving that higher concentration of matrix formed with PEG 6000 of ratio 1:5 increased the dissolution rate.

The increase in the in vitro characteristics can be attributed due to the formation of solid dispersion of paracetamol with carriers, with resulting size reduction. In addition to the size reduction of the crystalline substance, the faster dissolution rate of the drug may be due to excellent wettability and dispersability of drug from a solid dispersion system prepared with water soluble carriers. A comparative study of in-vitro dissolution profile of different ratios of paracetamol and its various carriers were studied.

ACKNOWLEDGEMENT

The authors are thankful to Apex laboratories, Chennai for providing free gift samples of Paracetamol. We thank Dr.ShanmugaPandiyan Principal, Mohamed Sathak A.J College of Pharmacy, for permitting to carry out the entire research work.

REFERENCES

1. Aulton's Pharmaceutics The Design and manufacture of medicine edited by Aulton Third edition page 293.
2. Noyes AA, Whitney WR. The rate of solution of solid substances in their own solutions. J Am Chem Soc 1897; 19:930-4.
3. Nernst W. Theorie der Reaktionsgeschwindigkeit in heterogenen systemen. Zeitschrift Physik Chemie 1904; 47:52-5.
4. Galia E, Nicolaides E, Horter D, Lobenberg R, Reppas C, Dressman B. Evaluation of various dissolution media for predicting in vivo performance of class I and II drugs. Pharm Res 1998; 15:698-705.
5. Sekiguchi K, Obi N. Studies on absorption of eutectic mixture. I.A comparison of the behavior of eutectic mixture of sulfathiazole and that of ordinary sulfathiazole in man. Chem Pharm Bull 1961; 9:866-72.
6. Serajuddin ATM. Bioavailability enhancement of poorly water soluble drugs by solid dispersion in surface active and self emulsifying vehicles. Bull Technique Gattefosse 1997; 90:43-50.
7. Leuner C, Dressman J. Improving drug solubility for oral delivery using solid dispersions. Eur J Pharm Biopharm 2000; 50:47-60.
8. Brahmankar DM, Jaiswal SB. Bioavailability and bio-equivalence biopharmaceutics and pharmacokinetics-A Treatise. 1Ed. New Delhi (India): Vallabh Prakashan; 1995.
9. Duncan QM, Craig. The mechanisms of drug release from solid dispersion in water soluble polymers. Int J Pharm 2002; 231:13144.
10. Tachibana T, Nakamura A. Method for preparing an aqueous colloidal dispersion of organic materials by using water-soluble polymers: dispersion of ß-carotene by polyvinylpyrrolidone. Kolloid-Z Polym 1965; 203:130-3.
11. Kearney AS, Gabriel DL, Mehta SC, Radebaugh GW. Effect of polyvinylpyrrolidone on the crystallinity and dissolution rate of solid dispersions of the anti inflammatory Ci-987. Int J Pharm 1994; 104:169-74.
12. Ahmad M, Fattah A, Bhargava HN. Preparation and invitro evaluation of solid dispersion of halofantrine. Int J Pharm 2002; 235:17-33.
13. Joshi H et al Bioavailability enhancement of poorly water-soluble drug by solid dispersion in polyethylene glycol-polysorbate 80 mixture. Int J Pharm 2004; 269:251-258.
14. Tripathy S, Sharma PK, Banthia AK. Preparation, characterization, invitro and in vivo evaluation of aceclofenac ointment. Ind J Pharm Sci 2005 Sep; 42(9):618-20.

Source of support: Nil, Conflict of interest: None Declared