ISSN: 0975-8232

IJPSR (2010), Vol. 1, Issue 7 (Research Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received 25 March, 2010; received in revised form 03 June, 2010; accepted 15 June, 2010

IMPROVEMENT OF DISSOLUTION BEHAVIOR OF PARACETAMOL USING SOLID DISPERSION TECHNIQUE

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Keywords:

Paracetamol,
Bioavailability,
Solid Dispersion,
Polyvinyl Pyrrolidone

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ABSTRACT

Paracetamol is an important anti-inflammatory and analgesic drug widely used in biological disorders. One of major problems with this drugs is its low solubility thus dissolution rate in biological fluid, which results into poor bioavailability after oral administration. In this study polyvinyl pyrrolidone (PVP) is used to enhance bioavailability of paracetamol. Paracetamol and PVP are used in 1:1 and 1:2 ratios to study the effect of PVP in dissolution profile of drug. Dissolution study showed a linear increase in paracetamol release with increase in polymer concentration. Two different batches of granules are also evaluated for their micromeritics properties and flow behavior**.** The micromeritics properties and dissolution profile showed a evident that PVP can be used to improve dissolution behavior of paracetamol.

INTRODUCTION: Oral bioavailability of a drug depends on its solubility and/or dissolution rate, therefore efforts to increase dissolution of drugs with limited water solubility is often needed [1]. Improvement in the dissolution rate of the poorly soluble drugs after oral administration is one of the most crucial challenges in modern pharmaceutics. Many methods are available to improve these characteristics including salt formation, micronization and addition of solvent or surface-active agents. Solid dispersion is one of these methods, which was most widely and successfully applied to improve the solubility, dissolution rates and consequently the bioavailability of poorly soluble drugs.

The solid dispersion is based on the concept that the drug is dispersed in an inert water-soluble carrier at solid state. Several water soluble carriers such as mannitol, urea, lactose, citric acid, polyvinyl pyrrolidone [2, 3, 4] and polyethylene glycols are used as carriers for solid dispersion. Tablets containing solid dispersion exhibited better dissolution profile then commercial tablets [5, 6, 7, 8, 9, 10]. Thus the solid dispersion technique can be successfully used for the improvement of dissolution of Paracetamol. Polyvinyl pyrrolidone has been used for the preparation of solid dispersion as a component of the binary system for various drugs such as Tenoxicam [11]. In this study polyvinyl pyrrolidone was selected and solid dispersion was prepared by the method of kneading.

MATERIALS AND METHODS:

Materials: Paracetamol was a generous gift from Ipca Laboratories, Mumbai. Polyvinyl pyrrolidone I.P grade were purchased from SD Fine Chemicals Ltd, Mumbai. All reagents were of analytical grade and supplied without need to purification. Double distilled water was used during the experiments.

Preparation of PVP-Paracetamol Solid Dispersion: A mixture of PVP and paracetamol (1:1 & 1:2) was wetted with water and kneaded thoroughly for 30 minutes in a glass mortar. The paste formed was dried under vacuum for 24 hours. Dried powder was passed through Sieve no. 60 and stored in a desecrator until further studied.

Preparation Ratio:

1:1 ratios of PCM and PVP (Batch A)

1:2 ratios of PCM and PVP (Batch B)

Percent Practical Yield (PY): Percentage practical yield was calculated to know about percent yield or efficiency of any method, thus its help in selection of appropriate method of production. SDs were collected and weighed to determine practical yield (PY) from the following equation.

PY (%) = Practical Mass (Solid dispersion) × 100 /Theoretical Mass (Drug + Carrier) ------ **(Equation 1)**

Drug Content: SDs equivalent to 10 mg of aceclofenac were weighed accurately and dissolved in the 10 ml of methanol. The solution was filtered, diluted suitably and drug content was analyzed at 275 nm by UV spectrophotometer [12]. The actual drug content was calculated using the following equation as follows:

% Drug content = Actual Paracetamol content in weight quantity of solid dispersion x 100/ Theoretical amount of Paracetamol in solid dispersion ---------- **(Equation 2)**

Micromeritic Study: Bulk density: Apparent bulk density (g/ml) was determined by placing pre-sieved bulk powder blend into a graduated

cylinder via a large cylinder and measuring the volume and weight of powder blend [12, 13, 14];

Bulk density= Weight of powder blend/volume of powder blend ---------- **(Equation 3)**

Tapped Density: It was determined by placing a graduated cylinder, containing a known mass of powder on mechanical tapping apparatus, which was operated for fixed number of taps (around 50). Using the weight of powder in a cylinder and its tapped volume, the tapped density was computed [12, 13, 14];

Tapped density= Weight of powder blend/tapped volume of powder blend ---------- **(Equation 4)**

Carr's Index: It is an important parameter to study compressibility behaviour of composites. Carr's index was calculated, from the results of bulk density and tapped density [12, 13, 14];

Carr's index = (bulk density-tapped density)/ tapped density ---------- **(Equation 5)**

Bulkiness: It is reciprocal of bulk density and calculated as [12, 13, 14];

Bulkiness= 1/ bulk density ---------- **(Equation 6)**

Angle of Repose: For the measurement of angle of repose, a glass funnel was taken with its tip at a given height (H), above a piece of graph paper placed on a horizontal surface. Powder was poured through the funnel until the apex of the conical pile touched the tip of the funnel. The angle of repose was calculated with the formula; tan θ= H/R, where θ is the angle of repose and R is the radius of the conical pile [12, 13, 14].

***In vitro* Drug Release Studies:** The release profile of an entrapped drug predicts how a delivery system might function and gives valuable insight into its *in vivo* behavior. *In vitro* release profiles for each SD as well as pure drug were performed using USP dissolution apparatus (Electro lab, Mumbai, India). Sample equivalent to 100 mg of paracetamol was added to 900 ml phosphate buffer of pH 7.4 at 37±0.5 ^{o}C and stirred at 100 rpm. Aliquot of 1 ml was withdrawn at time intervals of 5, 10, 15, 20, 30, 45 and 60 min. The withdrawn volume was replaced with the same volume of dissolution medium in order to keep the total volume constant. The absorbance of the samples was measured at 249 nm after suitable dilution if necessary, using appropriate blank.

RESULTS AND DISCUSSION: Solid dispersion of paracetamol was prepared using polyvinyl pyrrolidone and evaluated for various physical parameters. Percentage yield of the Paracetamol solid dispersion of ratio 1:1 and 1:2 was found to be 90% and 97.58% respectively. This illustrates the fact that, batch B releases more drug in comparison to batch A during same interval of time. The granules were also evaluated for drug content for both the batches. Drug content in the ratio of 1:1 & 1:2 was found to be 87% and 93.40% respectively which were fairly within the limits.

Prior to drug release and drug content studies, granules of each batch were characterized for physical parameters which involved bulk density, tapped density, consolidation index, Hausner's ratio and angle of repose. Result studies of these parameters are shown in table 1. Findings of study reveals the fact that granules of batch B have better flow behavior in comparison to that of batch

A. Good is the range of bulk density and tapped density, better is the ease of compaction in dosage form. This factor is thus of at most importance while studying the physical parameters. It can be also concluded on the basis of bulkiness data that, granules of batch B are lighter and hence provide a greater range of concentration to be incorporated in formulations. The values of all these parameters are illustrated in table 1.

TABLE 1: RESULT OF MICROMERITIC PARAMETERS AND FLOW BEHAVIOR

PARAMETERS	BATCH A (RATIO 1:1)	BATCH B (RATIO 1:2)
Bulk Density (g/cm^3)	0.45	0.48
Tapped Density (g/cm^3)	0.50	0.52
Bulkiness (cm^3/g)	2.23	2.02
Consolidation Index	0.1	0.07
Hausner Ratio	1.11	1.08
Angle of Repose	27.53^0	26.37^0

The dissolution behavior of both batches showed that batch B has better release characteristics as compared to batch A. In both the cases faster dissolution as compared to conventional dosage form is attributed to the fact that PVP forms molecular dispersions with drug molecules. The release data is shown in following figure 1. Thus the experiment showed that PVP can be used to improve the dissolution characteristics of poorly soluble drug in pharmaceutical formulations.

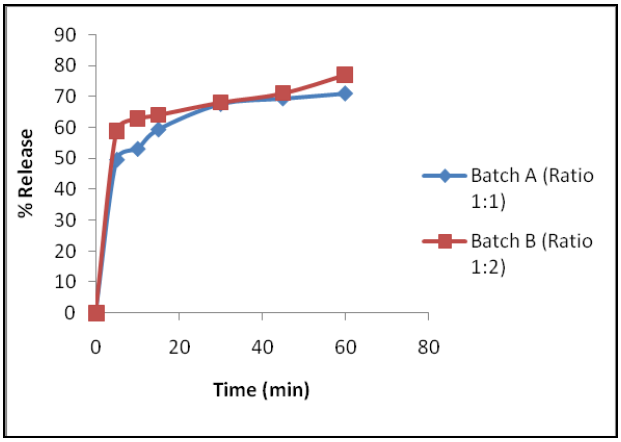

FIG. 1: RELEASE PLOT OF DRUG FROM SOLID DISPERSION

CONCLUSION: From the present study it can be easily demonstrated that, polyvinylpyrollidine has immense potential to improve solubility characters of any less soluble or poorly soluble drug. This work also illustrates the fact that PVP has characteristics to form molecular dispersions with the drug molecules, thereby, increasing the dissolulution rate of drug and decreasing the time of release of drug from the formulated mixture or granules.

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