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Research Article

EVALUATION OF ENHANCEMENT OF SOLUBILITY OF PARACETAMOL BY SOLID DISPERSION TECHNIQUE USING DIFFERENT POLYMERS CONCENTRATION

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ABSTRACT

Paracetamol (PCM) is a non-steroidal anti-inflammatory drug (NSAID), sparingly soluble and bitter in taste. It is 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 poorly water soluble non-steroidal anti-inflammatory drug, paracetamol , with polyethylene glycol 4000 (PEG 4000) and polyvinyl pyrrolidone (PVP) for enhancing the dissolution rate of the drug. The solid dispersions were prepared by physical mix method and kneading method at 1:1, 1:2 and 2:1 ratios of drug to polymer. The formulations were evaluated for percent practical yield, drug content, micromeritics and *invitro* dissolution studies. There is no interaction between drug and polymers. In this study it was indicated that there occurred an increase in *invitro* drug release for solid dispersion as compared to the pure drug taken alone. Based on the drug release pattern, the kneading method showed more drug release as compared to physical mix method. In physical mix method, the rate of dissolution of paracetamol was increased in PCM and PVP with the proportion of (1:2) when compared to the other formulations. In kneading method, the rate of dissolution of paracetamol was increased in PCM and PEG 4000 with the proportion of (1:2) when compared to the other formulations. Finally, solid dispersion containing PEG 4000, as a carrier, gave faster dissolution rates among all the formulations and was selected as the best formulation in this study.

Key words: Dissolution, solid dispersion, physical mix, paracetamol.

INTRODUCTION

Oral drug delivery is the easiest and simplest way of administering dosage form. Oral bioavailability of a drug depends on its solubility and/or dissolution rate. If these drugs are not completely released in the gastrointestinal tract, they will have a low bioavailability [1-4]. Drug release is a crucial and limiting step for oral drug bioavailability, particularly for drugs with low gastrointestinal solubility and high permeability. Thus, efforts to increase dissolution of drugs with limited aqueous solubility are often required [5]. Improvement of aqueous solubility of such drugs is one of the major concerning factors of the pharmaceutical industries [6-8].

Many methods are available to improve these characteristics including salt formation, solid dispersions, micronization and addition of solvent or surface-active agents. Solid dispersions are one of the most successful strategies to improve drug release of poorly soluble drugs [7, 9, 10].Solid dispersions are molecular mixtures of poorly aqueous soluble solid drug in an inert hydrophilic carrier. Drug release profile from such mixtures is driven by the polymer properties [11].

Diverse water-soluble carriers such as polyethylene glycols (PEG 4000 and PEG 6000), polyglycolized fatty acid ester, polyvinyl pyrollidone K 25 (PVP), poloxamers, polyols (mannitol, sorbitol), organic acid (citric acid) and hydrotopes (urea, nicotinamide) are used as carriers for solid dispersion [12, 13, 14, 15]. Among these PEG and PVP are the most widely used carriers in solid dispersions [16]. There are various methods for preparing solid dispersion which includes the melting method, the solvent method, fusion method, physical mixture, kneading method, super critical fluid method, etc [17].

MATERIALS AND METHODS

Materials: Paracetamol (PCM) was of pharmaceutical grade sample, gift from Ipca Laboratories, Mumbai. Polyvinyl pyrrolidone (PVP) I.P grade and polyethylene glycol (PEG 4000) were purchased from SD Fine Chemicals Ltd, Mumbai. All reagents and solvents were of analytical grade and supplied without need to purification.

Methods

Preparation of PVP-paracetamol and PEG 4000-paracetamol Solid Dispersion

a) Preparation of physical mixture

The physical mixture of paracetamol - PVP and paracetamo l- PEG 4000 each were prepared in 1:1, 1:2, 2:1 ratios by mixing accurately weighed amounts of drugs and various carriers with the help of a spatula in a glass mortar.

b) Preparation by kneading method

The required amount of paracetamol and carrier in 1:1, 1:2 & 2:1 rat io were wetted with sufficient volume of methanol 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 desiccators until further evaluation.

Preparation Ratio

Physical mix method

1:1 ratios of PCM and PEG 4000 (F1)

1:2 ratios of PCM and PEG 4000 (F2)

2:1 ratios of PCM and PEG 4000 (F3)

1:1 ratios of PCM and PVP (F4)

1:2 ratios of PCM and PVP (F5)

2:1 ratios of PCM and PVP (F6)

Kneading method

1:1 ratios of PCM and PEG 4000 (F7)

1:2 ratios of PCM and PEG 4000 (F8)

2:1 ratios of PCM and PEG 4000 (F9)

1:1 ratios of PCM and PVP (F10)

1:2 ratios of PCM and PVP (F11)

2:1 ratios of PCM and PVP (F12)

Physical characterization

Determination of Percent Practical Yield (PY):

To determine the efficiency of any method of production, Percentage practical yield was calculated. In this method pre-weighed solid

dispersions were collected to determine practical yield (PY) from the following equation.

Percent Practical Yield (PY) = (Weight of Practical solid dispersions × 100)/ Theoretical weight (paracetamol + Polymer)

Drug Content

Dissolve 100 mg of Solid dispersions 10 ml of methanol. The solution was filtered, diluted suitably and analyzed at 257 nm by UV spectrophotometer. The actual drug content was calculated as follows:

Percent Drug content = (Actual paracetamol content in weighed quantity of solid dispersions x 100)/Theoretical amount of paracetamol in solid dispersion

Micromeritic characterization

Determination of Bulk density: The pre-sieved bulk powder blend was weighed. It was then placed in a graduated cylinder and the volume was measured. This gives the relationship to determine the apparent bulk density (g/ml)

Apparent bulk density = Weight of powder blend/volume of powder blend

Determination of Tapped density: The pre-weighed amount of powder blend was placed in a graduated cylinder and tapped for fixed number of taps (around 50) on mechanical tapping apparatus. From this the tapped volume was noted. Finally the tapped density was computed.

Tapped density = Weight of powder blend/tapped volume of powder blend

Determination of Carr's Index: It was used to determine the compressibility of powder blends from the results of bulk density and tapped density.

Carr's index = (Tapped density - Apparent bulk density)/Tapped density

Determination of Bulkiness: It was calculated mathematically as the reciprocal of apparent bulk density.

Bulkiness = 1 / Apparent bulk density

Determination of Angle of Repose: It was determined through funnel method. A glass funnel with its tip at a given height (H), above a piece of graph paper was placed on a horizontal surface. Powder was poured through the funnel such that the apex of the conical pile touched the tip of the funnel. The angle of repose (θ) was then calculated as follows:

$$\tan \theta = H/R$$

where, R is the radius of the conical pile.

Determination of Dissolution profile

Invitro release profiles for each batch was performed using USP dissolution apparatus (Electro lab, Mumbai, India). Solid dispersions of Paracetamol prepared by both the techniques was kept in the basket of dissolution apparatus and immersed in 900 ml distilled water at 37 ± 0.5° C and stirred at 100 rpm. Aliquot of 5 ml was withdrawn at time intervals of 5, 10, 15, 20, 30, 45 and 60 min. The same amount of withdrawn volume was replaced with the dissolution medium in order to maintain the sink condition. The sample withdrawn was analyzed at 257 nm spectrophotometrically.

RESULTS AND DISCUSSION

Solid dispersions of Paracetamol were prepared with PEG 4000 and PVP using physical mix method as well as kneading method. Percentage yield and percent drug content of all formulations formed was determined and it was found that percent practical yield and percent drug content was estimated to be 97.01% and 98.23% respectively in case of F8 formulation and 93.67% and 96.45% in case of F5 formulation.

The data illustrates the fact that, formulation, F5 and F8 releases more drugs in comparison to other formulations during same time interval. The granules were also evaluated for drug content for all the formulations. Drug content in the ratio of 1:1, 1:2 and 2:1 was found for each polymer using both methods respectively which were fairly within the limits. Drug content studies were performed and evaluated before drug release using granules of each formulation. Following parameters were characterized 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 reveal the fact that granules of both have better flow behaviour. Good is the range of bulk density and tapped density, better is the ease of compaction in dosage form. This factor is thus of utmost importance while studying the physical parameters. It can be also concluded on the basis of bulkiness data that, granules of formulation, F5 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 and table 2.

Figure -1: Dissolution profile of PEG 4000 and paracetamol by physical mix and kneading method

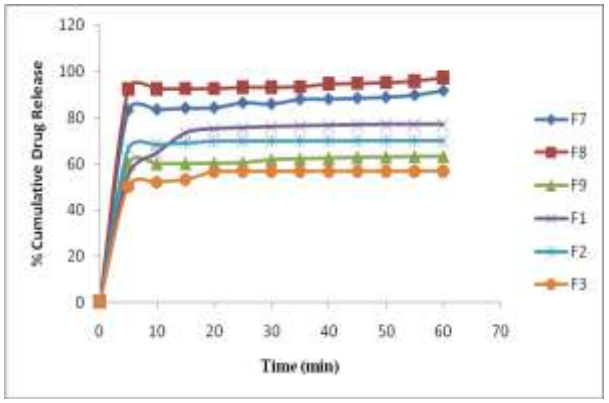
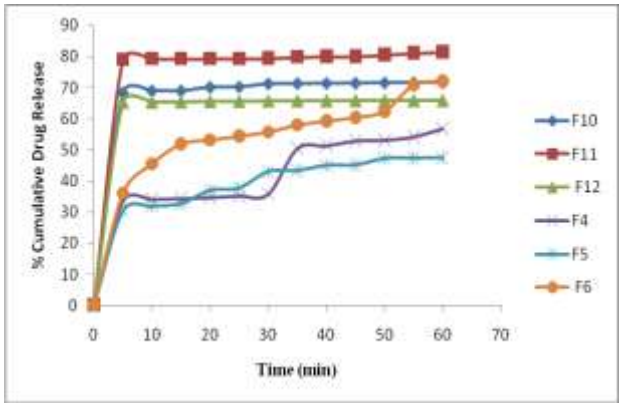


Figure 2. Dissolution profile of PVP and paracetamol by physical mix and kneading method



The dissolution behaviour showed that formulations prepared by kneading method has better release characteristics as compared to the formulations prepared by physical mix method. Dissolution rate for solid dispersions were greater in case of PCM and PEG 4000 as compared to all other formulations of PCM and PVP in different ratios and the ratio 1:2 PCM and PEG 4000 prepared by kneading method showed the greatest release profile than all other formulations. The release data is shown in following figure 1 and figure 2. Thus the experiment showed that PEG 4000 and kneading method can be used to improve the dissolution characteristics of poorly soluble drug in pharmaceutical formulations.

Table -1: Micromeretic parameters using physical mix method

PARAMETERS	F1	F2	F3	F4	F5	F6
Apparent Bulk Density (g/cm)	0.32	0.41	0.38	0.43	0.48	0.37
Tapped Density (g/cm)	0.34	0.46	0.4	0.46	0.49	0.42
Bulkiness (cm/g)	3.13	2.44	2.63	2.17	2.04	2.38
Carr's Index	0.06	0.11	0.05	0.07	0.02	0.12
Hausner's Ratio	1.06	1.12	1.05	1.07	1.02	1.14
Angle of Repose	21.32°	19.39°	20.76°	24.70°	22.78°	28.12°
Practical yield (%)	77.08	78.48	81.12	92.01	93.67	84.63
Drug content (%)	90.13	83.02	83.87	94.01	96.45	87.31

Table -2: Micromeretic parameters using kneading method

PARAMETERS	F7	F8	F9	F10	F11	F12
Apparent Bulk Density (g/cm)	0.31	0.34	0.28	0.33	0.35	0.26
Tapped Density (g/cm)	0.32	0.38	0.33	0.37	0.4	0.27
Bulkiness (cm/g)	3.23	2.94	3.57	3.03	2.86	3.85
Carr's Index	0.03	0.11	0.15	0.11	0.13	0.4
Hausner's Ratio	1.03	1.12	1.18	1.12	1.14	1.04
Angle of Repose	19.12°	22.42°	20.33°	19.42°	17.35°	22.18°
Practical yield (%)	84.23	97.01	89.42	85.32	88.21	86.03
Drug content (%)	83.15	98.23	89.76	88.03	90.06	87.77

CONCLUSION

The major problem of paracetamol is its very low solubility in biological fluids. From the present study it can be easily demonstrated that PEG 4000 has immense potential to improve solubility characters of any less soluble or poorly soluble drug. The results revealed that it is possible to enhance the dissolution rate of paracetamol by increasing the surface area of the drug by solid dispersion method. Formulation prepared by kneading method using paracetamol and PEG 4000 of ratio 1:2 (F8) yielded best results in terms of dissolution rate. This work also illustrates the fact that PEG 4000 has more characteristic to form molecular dispersions with the drug molecules, thereby increasing the dissolution rate of drug and decreasing the time of release of drug from the formulated mixture.

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