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TERNARY SOLID DISPERSIONS OF OMEPRAZOLE FOR ENHANCING SOLUBILITY AND DISSOLUTION.

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ABSTRACT

Omeprazole, is widely used in the treatment of acid, peptic disorders and duodenal ulcers. One of the major problems with this drug is its low solubility in biological fluids, which results into poor bioavailability after oral administration. Therefore to increase its aqueous solubility ternary solid dispersions (TSD) of omeprazole were prepared by solvent evaporation method, using hydrophilic carriers like polyvinyl pyrrolidone (PVP), hydroxyl propyl methyl cellulose (HPMC), and solubilizer sodium lauryl sulphate (SLS). Eight formulae were prepared and evaluated for drug content, solubility, In-vitro drug release and dissolution efficiency. Solid state characterization including FTIR and XRD is also carried out. All formulae showed marked significant improvement in the solubility and dissolution rate of the drug. Solubility studies indicated that PVP along with SLS significantly increased the solubility as well as the bioavailability of omeprazole by 14.66 folds. The interaction studies showed no interaction between the drug and any of the used carriers. In-vitro release profiles of all dispersions were comparatively evaluated and also studied against pure omeprazole. Faster dissolution with greater dissolution efficiency was exhibited by ternary solid dispersion (F7) containing omeprazole: PVP: SLS in 1:1:0.75 ratios. The cumulative release of omeprazole from formulation F7 was 98.15% within 60 min and was 4.48 times higher than the pure drug

in 0.1N HCl. The increase in dissolution rate of omeprazole by ternary dispersion technique may be due to increase wettability and hydrophilic nature of carrier.

KEYWORDS: Omeprazole, ternary solid dispersion, solvent evaporation method, Solubility.

INTRODUCTION

A large percentage of potential drug candidates suffer from low aqueous solubility and/or low dissolution rate. This results in low drug concentrations at the absorptive sites and hence low oral availability. Amidon et al. classified such drugs in the biopharmaceutical classification system as class II compounds. The formulation of solid dispersions of BCS II compounds either by co-precipitation of drug and carrier from a common solvent or by co melting and quench cooling is a popular strategy to reduce the drug particle size and hence increases dissolution rate.[1] The dissolution rate is affected by state and size of the particle and carrier with in which it is enclosed. Small size of the drug particles cause increased surface area which helps in enhancement of drug dissolution. Amorphous state of the drugs increased solubility of the drug and hydrophilic carrier enhances wetting characteristics of the drugs which ultimately leads to increased dissolution rate of drugs in solid dispersions.[2] But solid dispersions have disadvantages like phase separation, crystal growth or conversion from the amorphous to the crystalline state during storage inevitably leading to reduced dissolution rates.[3]

Surfactants lower the interfacial tension between a drug and the dissolution medium and there by promote wetting of a drug. The addition of surfactants in solid dispersions leads to the formation of a ternary system, called Ternary solid dispersions (TSD) which enhances the solubility and dissolution of poorly soluble drugs. Ternary solid dispersions are defined as the dispersion of active ingredients in an inert carrier matrix of surfactant and polymers. In TSD carriers reduce molecular mobility and prevent recrystallization. Moreover hydrophillic polymers are able to enhance drug super saturation, surfactant decrease aggregation, improve wetting, and increases dissolution of drug.[4,5] Polyvinyl pyrrolidone has been widely used as a carrier for solid dispersions of drugs such as furosemide.[6] oxaprozin[7] nimodipine.[8] and albendazole.[9] Hydroxypropylmethylcellulose as a carrier enhanced enhanced solubility and bioavailability of various drugs like itraconazole.[10] sibutramine.[11] and curcumin.[12] Omeprazole is a proton pump inhibitor that suppresses gastric acid secretion by specific inhibition of the H+/K+- ATPase in the gastric parietal cell. By acting specifically on the proton pumpomeprazole blocks the final step in acid production.[13] The drug is used in

conditions where the inhibition of gastric acid secretion may be beneficial, including aspiration syndromes, dyspepsia, gastro-oesophageal reflux disease, peptic ulcer disease, and the Zollinger Ellison syndrome.[14] But it does not show comprehensive therapeutic effect because of its poor solubility and dissolution, which leads to poor bioavailability of the drug.

In the present investigation TSD of omeprazole were prepared by physical mixture and solvent evaporation method, employing various carriers like polyvinyl pyrrolidone (PVP K25), hydroxyl propyl methyl cellulose (HPMC 15cps), and sodium lauryl sulphate (SLS) as surfactant for enhancing the solubility and dissolution rate.

MATERIALS AND METHODS

Materials

Omeprazole was obtained as a gift sample from Bangalore fine chemicals, India. Polyvinyl pyrrolidone (PVP K25), hydroxyl propyl methyl cellulose (HPMC15cps), and sodium lauryl sulphate (SLS) were obtained from lobachem. Pvt Ltd., SD fine chem. ltd., and fisher scientific, Mumbai, India respectively. All other chemicals and solvents were of analytical grade.

METHODS

Preparation of omeprazole TSD

Ternary dispersions of omeprazole in were prepared using like PVP, HPMC as carriers and SLS as ternary agent. In formulations ratio of drug: carrier was maintained in constant ratio of 1:1 and SLS concentration was varied as shown in Table 1. The methods used for preparation of these dispersions were physical mixing and solvent evaporation methods.

Table 1: Formulation table of omeprazole ternary solid dispersions.

Formulation code	Omeprazole	SLS	HPMC (15cps)	PVP K25
F1	1gm	25mg	1gm	-
F2	1gm	50mg	1gm	-
F3	1gm	95mg	1gm	-
F4	1gm	-	1gm	-
F5	1gm	25mg	-	1gm
F6	1gm	50mg	-	1gm
F7	1gm	95mg	-	1gm
8	1gm	-	-	1gm

Physical mixture

The physical mixtures were prepared by weighing the calculated amounts of omeprazole, carriers and SLS, then mixing them in a glass mortar by triturating. The resultant physical mixtures were passed through 44-mesh sieve and stored in desiccator until used for further studies.

Solvent evaporation method

omeprazole and carriers were dissolved separately in minimum quantity of acetone, mixed. Ternary agent SLS was dispersed in the solution. The solution was evaporated on temperature controlled water bath to get the solid mass which was then passed through sieve no.44 and stored till further evaluations.

Saturation solubility study: Solubility study was conducted as per the method reported by Higuchi and Connors. Excess quantity of the drug and TSD were taken for study. The solubility of omeprazole in pure drug and TSD was determined in 0.1N Hcl. Drug and TSD were weighed accurately and added to solvents in screw capped bottles separately. The bottles were shaken in an orbital shaker at 37 ^{0}C for 24 hrs. The sample was then filtered through Whatman filter paper and the filtrate was assayed spectrophotometrically at 281 nm.[15]

Drug content: TSD 50 mg was accurately weighed and dissolved in 100ml of buffer (0.1N Hcl) and filtered. Filtered solution was suitably diluted and absorbance was measured with a UV-visible spectrophotometer (Pharmaspec 1700, Shimadzu, Japan) at 281 nm.

Solubility studies: Solubility study was conducted as per the method reported Higuchi and Connors. Excess quantity omeprazole TSD and physical mixtures were weighed accurately and added to 10ml of in water and 0.1N Hcl in screw capped bottles. The bottles were shaken in an orbital shaker at 37 ^{0}C for 24 hrs. Then the solutions were filtered, and concentration of drug was determined by UV-visible spectrophotometer at 281 nm.

In-vitro dissolution studies: Omeprazole pure drug, physical mixtures and TSD equivalent to 20 mg omeprazole were subjected to in-vitro dissolution studies using USP Dissolution test apparatus II (paddle type) at 37±0.5^{0}C using 900ml 0.1N Hcl as dissolution media. The rotation speed of the paddle was adjusted to 50rpm. Samples were collected at 5, 10, 20, 30, 45 and 60 minutes, passed through a 0.45µm filter and analyzed by direct UV visible

spectrophotometer at 281nm. Each preparation was tested in triplicate and the mean values were calculated. The cumulative drug release was calculated and plotted versus time.[16]

Model Independent Approaches

(a) Dissolution Efficiency: Dissolution efficiency (DE) represents the area under the dissolution curve at time t (measured using the trapezoidal rule) and expressed as percentage of the area of the rectangle described by100 % dissolution in the same time.[17]

$$D.E. = \frac{\int_0^t y \times dt}{y_{100} \times t} \times 100\%$$

Where y is the drug percent dissolved at time t

(b) Initial dissolution rate (%/min)

To compare dissolution rate enhancement of omeprazole from TSDs formulae, Initial dissolution rate (IDR) was calculated as percentage dissolved of drug over the first 5 minutes per minute.[17]

FTIR: FTIR was used to access interaction between drug and carrier molecules used in formulation. The IR spectra were recorded using a FTIR spectrophotometer. The moisture free samples were scanned over the frequency range of 4000 to 400cm.$^{-1}$ FTIR spectra of selected formulation and physical mixtures were recorded.

X-ray diffraction (XRPD)

The crystallinity of Omeprazole pure drug, physical mixtures and TSD was investigated by XRPD using Bruker diffractometer (WI 1140, Japan) and Cu-Kα radiation. The diffractograms were run at 2.5 °C min^{-1} and chart speed of 2°/2 cm per 2θ angle.

RESULTS AND DISCUSSION

Solubility studies: Table 2 summarizes the experimentally determined solubility of omeprazole, and its TSDs in 0.1N Hcl. With a solubility of 0.15mg/ml (at 37^{o}c), omeprazole is clearly poorly soluble. TSD prepared by solvent evaporation method with incorporation of HPMC, PVP along with SLS as ternary agent showed solubility enhancement up to 1.86mg/ml, and 2.28 mg/ml respectively. Solubility was also found to increase in biorelevant media as they contain hydrophilic polymers and SLS. The surfactant is likely to exert micellar solublization effect on the omeprazole. In formulation F7 the omeprazole solubility

increased by 14.66 folds. The combined effect of hydrophilic polymers and SLS in the TSD has produced significant enhancement in the solubility of omeprazole. The mechanism for solubility enhancement by TSD is reported because of increased surface area due to reduction in particle size of drug and wetting, solublizing effect of the carrier.

Drug content: The drug content in was found to be in the range of 99-97% in formulations F1-F4 containing HPMC, it was 100-98% in formulation F5-F8 containing PVP as shown in table 2. The results indicate high content uniformity in the omeprazole TSD.

Table 2: Results of solubility and drug content of omeprazole TSD

Formulation code	Solubility (mg/ml) in 0.1N Hcl (average ±S.D)	% Increase in solubility	Drug content average (% ± S.D)
F1	1.266 ±0.24	844	98.199±0.13
F2	1.630 ±0.25	1086.6	98. 996 ±0.86
F3	1.861±0.08	1240.6	99.599±0.22
F4	1.194 ±0.24	996	97.643±0.91
F5	1.354 ±0.36	902.6	98. 981±0.05
F6	1.863 ±0.29	1242	99.196±0.88
F7	2.280 ±0.26	1520	100.692±0.15
F8	1.296 ±0.36	864	99.292±0.81
Pure omperazole	0.15±0.08	-----	------

In-vitro dissolution studies

The dissolution profiles of omeprazole, physical mixtures and TSD prepared with hydrophilic polymers and surfactant were determined in 0.1N HCL. The release profiles were plotted as the percentage drug dissolved versus time. From release profile plots it is evident that the rate of dissolution of pure omeprazole in 0.1N HCL was slow and showed release of 21.89% within 60 min. Formulation F1-F4 containing HPMC as a carrier showed drug release in the range of 93-74.4% in 60min. Formulation F5-F8 PVP as a carrier showed drug release in the range of 98.15-80.14% in 60 min. Among all formulations F1-F8 best formulation were selected for each carrier basing on maximum drug release within 60 min. The best formulations are F3 (93% drug release) containing HPMC, and F9 (98.15% drug release) containing PVP. The drug dissolution in formulations increased with gradual increase in amount of surfactant SLS. Physical mixtures of best formulations PM 3 released 53.88% and PM 7 released 58.57% in 60 min. Figures 1& 2 shows the dissolution profiles of pure omeprazole and its physical mixtures and TSD respectively.

Hence, the TSD prepared by solvent evaporation method showed faster release of omeprazole compared to dispersion obtained by physical mixture technique. This may be due to the fact that ternary dispersion prepared by solvent evaporation method result in a more uniform dispersion of the drug in the hydrophilic carriers (PVP) matrix as compared to those prepared by physical mixture technique.

The increase in dissolution from the solid dispersion was due to the solublizing effect of the carrier, which forms a hydrophilic interfacial layer between the drug particles and the dissolution medium, thus leading to a higher dissolution rate. When solid dispersion consisting of an insoluble drug and a highly water soluble carrier with surfactants was dissolved in aqueous medium, the carrier would dissolve rapidly, leaving the insoluble drug in an extremely fine state of subdivision. The large surface area of the resulting suspended particles might have resulted in an enhanced dissolution rate and improved bioavailability.

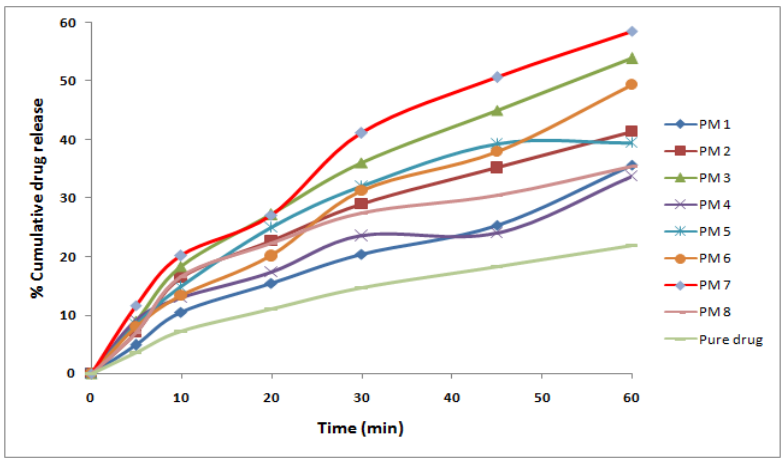

Figure 1: Dissolution profiles of omeprazole TSD prepared by physical mixture method.

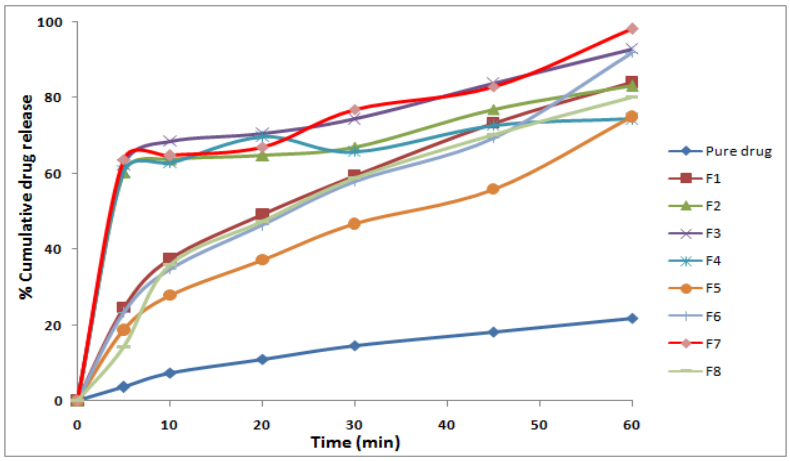

Figure 2: Dissolution profiles of omeprazole TSD prepared by solvent evaporation method

Model Independent Approaches

The calculated $\%DE_{5min}$, $\%DE_{30min}$, $\%DE_{60min}$ and IDR values are presented in table 3. The average percentage release of pure drug was 21.87% in 60 min and it is obvious from %DE 30min of 14.65 and IDR of 0.72 %/min that the dissolution of pure omeprazole is poor and slow and this was attributed to the hydrophobicity of the drug. Formulation of omeprazole as ternary solid dispersion with either HPMC or PVP resulted in significant enhancement of omeprazole dissolution and this is clear from the values of $\%DE_{5min}$, $\%DE_{30min}$, $\%DE_{60min}$ and IDR compared to the pure drug (table 3). The results obtained revealed that all ternary solid dispersions of omeprazole have faster dissolution than pure omeprazole. Of note is the fact that the extent of enhanced dissolution depended on the concentration of the polymer used in the solid dispersion, increasing the polymer concentration leaded to increasing the drug release. Formulae prepared with PVP showed higher dissolution rates than those prepared with HPMC and this may be explained as the PVP produced less viscous dispersion and the rapid diffusion of the dissolved drug molecules.

Table 3: Dissolution parameters obtained from dissolution data of different TSD formulae.

Formulation code	Dissolution Parameters			
	$\%DE_{5min}$	$\%DE_{30min}$	$\%DE_{60min}$	IDR(%/min)
Pure drug	3.6±0.08	14.65±0.41	21.87±0.21	0.72±0.25
F1	4.83±0.05	59.3±0.23	80.05±0.54	0.97±0.36
F2	7±0.02	62.05±0.58	83.09±0.2	1.40±0.15
F3	8.92±0.12	74.4±0.61	93±0.65	1.78±0.2
F4	9.14±0.16	55.8±0.35	74.4±0.81	1.83±0.6
F5	8.31±0.09	46.68±0.71	80.14±0.51	1.66±0.8
F6	8±0.054	67.88±0.84	91.98±0.21	1.60±0.51
F7	11.59±0.02	77.05±0.21	98.15±0.16	2.32±0.16
F8	7.08±0.025	58.76±0.19	74.96±0.54	1.42±0.21

FTIR spectroscopy data

The FTIR spectrum of pure drug, TSD best formulation F7 and its PM 7 are presented in figure 3(a, b, c) respectively. Pure drug shown sharp characteristic bands at 3352, 125 9, 1620, 2921,119 $9cm^{-1}$ due to stretching vibration bands of N-H, S=O, C=N, C-H, O-C respectively. FTIR spectra of the F 7 and PM 7 show the characteristic bands of the drug with negligible change in intensity and this may be due to the dilution factor of the mixture by the carrier. The FTIR study revealed no physical or chemical interactions of omeprazole with PVP and SLS.

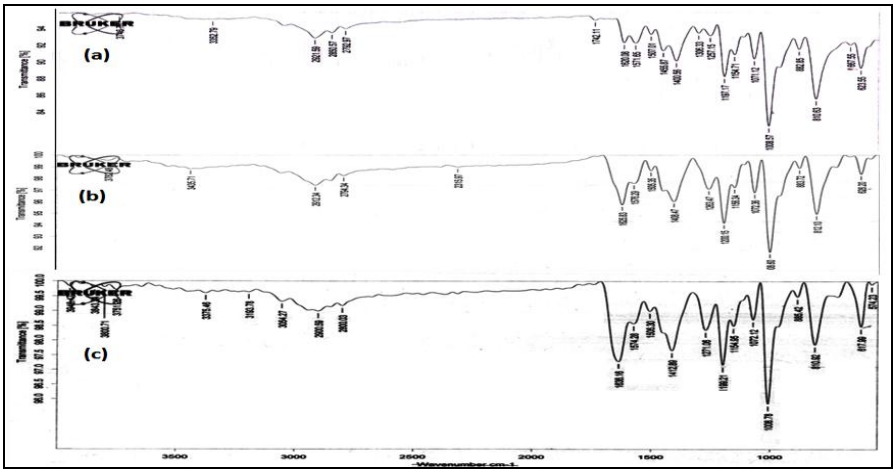

Figure 3: FTIR spectra of (a) pure omeprazole, (b) PM 7, (c) TSD best formulation F7.

XRPD Studies: The X-Ray diffraction pattern for omeprazole and TSD are depicted in Figure 4 and showed marked crystallinity as evident from the sharp peaks at 2θ angles of 9.12º, 12.4º, 1 9.34º and 23.98º. The degree of crystallinity is seen to be decreased and it depends on the processing method. The XRPD of TSD prepared by physical mixture shows higher degree of crystallinity as compared to those prepared by solvent evaporation method as evident from the disappearance of the sharp peaks. This could be attributed to the rapid evaporation of solvent from the solution seemingly interferes with the crystal building process leading to amorphization of the drug, consequently increased the drug solubility.

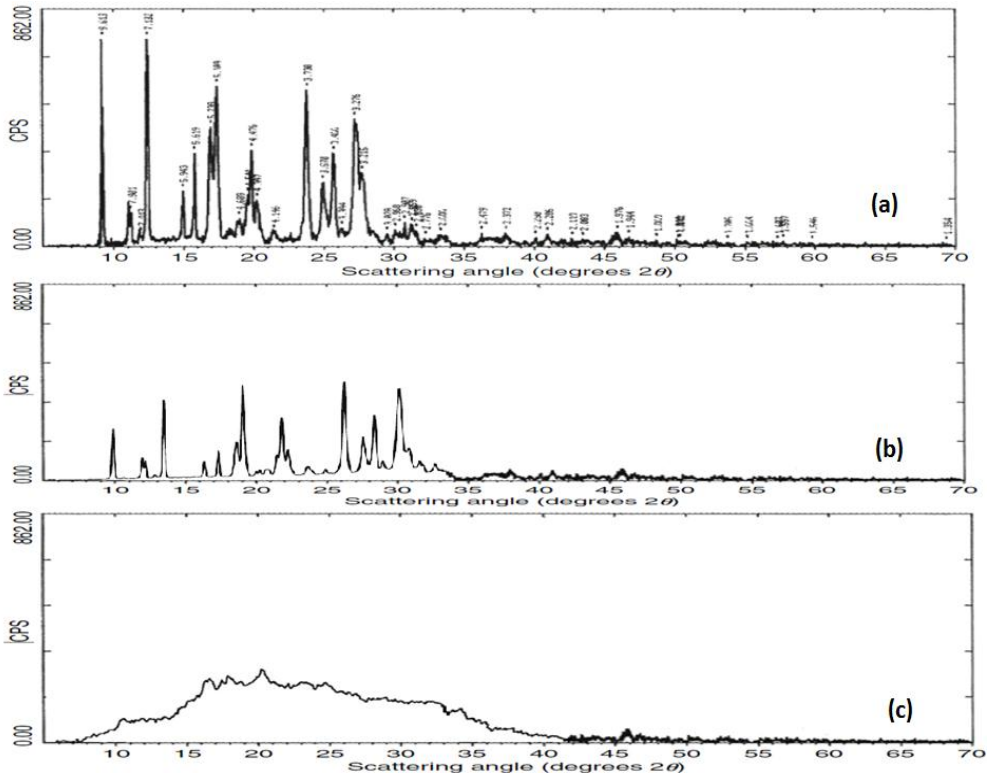

Figure 4: XPRD spectra of (a) pure omeprazole, (b) PM 7, (c) TSD best formulation F7.

CONCLUSION

TSDs of omeprazole prepared by solvent evaporation method possessed dramatically higher solubility & dissolution rates as compared to pure omeprazole and dispersions prepared by physical mixture method. The FTIR study indicated no chemical interaction between drug and excipients. The intermolecular interactions between drug and carriers leading to better dispersion of drug in the polymer matrix, reduction in size of drug particles, increase in the amorphous nature, increase in wettablity and decrease in surface tension resulted in enhanced dissolution of the drug from the ternary dispersion system. PVP K25 along with SLS exerted synergistic effect to enhance solubility as well as dissolution of poorly soluble omeprazole drug.

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