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PREPARATION AND CHARACTERIZATION OF POLAXAMER BASED SOLID DISPERSION FOR EFFECTIVE ENHANCEMENT OF SOLUBILITY OF POORLY WATER SOLUBLE DRUG

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ABSTRACT

Poorly soluble drugs represent a problem for their scarce availability related to their low dissolution rate. The major drawback of low aqueous solubility is delays its absorption from the gastrointestinal tract.Solubility behavior of a drug is one of the key determinants of its oral bioavailability.Celecoxib is a highly poorly water-soluble nonsteroidal anti-inflammatory drug (NSAID) with relatively low bioavailability,able to selectively inhibit cyclooxygenase-2 (COX-2).The aim of the present study was to enhance the solubility and dissolution rate of Poorly water soluble by a solid dispersion method using various hydrophilic carriers such as poloxamer 407, PVP, HPMC and PEG were screened. Poloxamer 407was most effective to form a superior solid dispersion of celecoxib having significantly enhanced solubility. Particularly, solid dispersion of celecoxib with poloxamer 407 in the weight ratio of 1:4 prepared by melting solvent method enhanced the solubility of celecoxib to the greatest extent. Poloxamer 407 based solid dispersion showed 65 times higher (0.513 mg/ml) solubility then pure celecoxib whereas solid dispersion of celecoxib with PVP, HPMC and PEG were showed 31 times (0.248mg/ml), 38 times (0.304mg/ml) and 23.5 times (0.182mg/ml) higher solubility than pure celecoxib, respectively However, it exhibited poor physical stability and due to hygroscopic nature of poloxamer 407, solid dispersion showed 10% drug degradation on 45days storage. To avoid this unstable form of poloxamer based solid dispersion, HPMC, PEG-8000, PVP-K30 and their combination were incorporated as an adsorbent of hygroscopic nature and inhibitor the recrystallization of drug. The solid dispersion of celecoxib was characterized by FT-IR, SEM (scanning electron microscopy), (DSC) differential scanning calorimetery, drug content, and *in-vitro* dissolution profile. The significant enhancement in aqueous solubility of celecoxib achieved by solid dispersion technique opens up the possibility of development of oral dosage form with improved bioavailability employing the technique.

K**eywords** Solid dispersion, Celecoxib, Polaxamer, Solubility enhancement, HPMC, PVP.

INTRODUCTION

Poorly soluble drugs represent a problem for their scarce availability related to their low dissolution rate[1,2]. The major drawback of low aqueous solubility is delays its absorption from the gastrointestinal tract[3]. Solubility behaviour of a drug is one of the key determinants of its oral bioavailability. Solid dispersions are one of the most promising strategies to improve the oral bioavailability of poorly water soluble drugs[4]. By reducing drug particle size to the absolute minimum, and hence improving drug

wettability, bioavailability may be significantly improved [5,6.]. The objective of the work relates to increase the solubility and dissolution rate of celecoxib (model drug) by novel solid dispersion technique. The application of dispersions is one of the strategies applied to increase the dissolution rate of lipophilic drugs in aqueous environments. They consist of a hydrophilic carrier incorporating very small particles of the lipophilic drug, preferably in the amorphous state. The solid dispersion method is one of the effective approaches to achieve the goal of solubility enhancement of celecoxib in the lab scale and can be used at industrial scale also. The work also elaborated the solubility effect on celecoxib in solid dispersion by using various alternative polymers and their combination.

MATERIALS AND METHODS

Celecoxib was a gift sample from M/s. Sigma Laboratories, Mumbai, methanol (Qualigens) and polyvinylpyrrolidone (PVP K30) was a gift sample from M/s. Sun Pharma Ind. Ltd., Mumbai. Poloxamers or pluronic (marketed by BASF corporation) and Hydroxypropyl methylcellulose (HPMC), and Polyethyl glycol were procured from commercial sources. All other materials used were of pharmacopoeial grade.

Method of preparation

Preparation of Polymeric combination based Solid dispersion by melting solvent evaporation method in which the accurately weighed amount of poloxamer-407 melted at 56-57ºC in china dish and solution of celecoxib (in ethanol) was added into melted carrier with continuous stirring to obtained the clear solution and added drop wise the ethanolic solution of PVP-K30, HPMC and PEG along with and different concentration in this solution with continuous stirring to obtain the solidified viscous mass and rapid cooled in ice-bath and stored at room temperature for 24 hrs[7,8]. Dried dispersion was ground in a pestle mortar and sieved through 44# sieve.

Estimation of celecoxib[9,10,11]

Spectrophotometric method based on the measurement of absorbance at 251 nm in water containing 1% sodium lauryl sulphate was used in the present study for the estimation of celecoxib. The method was validated for reproducibility, accuracy, precision and linearity by analyzing six individually weighed samples of celecoxib. The stock solution of celecoxib was subsequently diluted to a series of dilution containing 5, 10, 15, 20 and 25 µg/ml of solution, using distilled water containing 1% sodium lauryl sulphate. The absorbance of these solutions was measured in UV-VIS spectrophtometer (Simadzu 1700). The method obeyed Beer's law in the concentration range of 0-25 µg/ml.

Table 1 - Solubility of celecoxib in solid dispersion using various hydrophilic carriers

S. NO	Drug : hydrophilic carrier	Solid dispersion with PVP	Solid dispersion with HPMC	Solid dispersion with PEG	Solid dispersion with Poloxamer
1	1:1	0.164	0.152	0.080	0.288
2	1:2	0.203	0.208	0.104	0.384
3	1:3	0.232	0.248	0.176	0.502
4	1:4	0.248	0.304	0.182	0.513

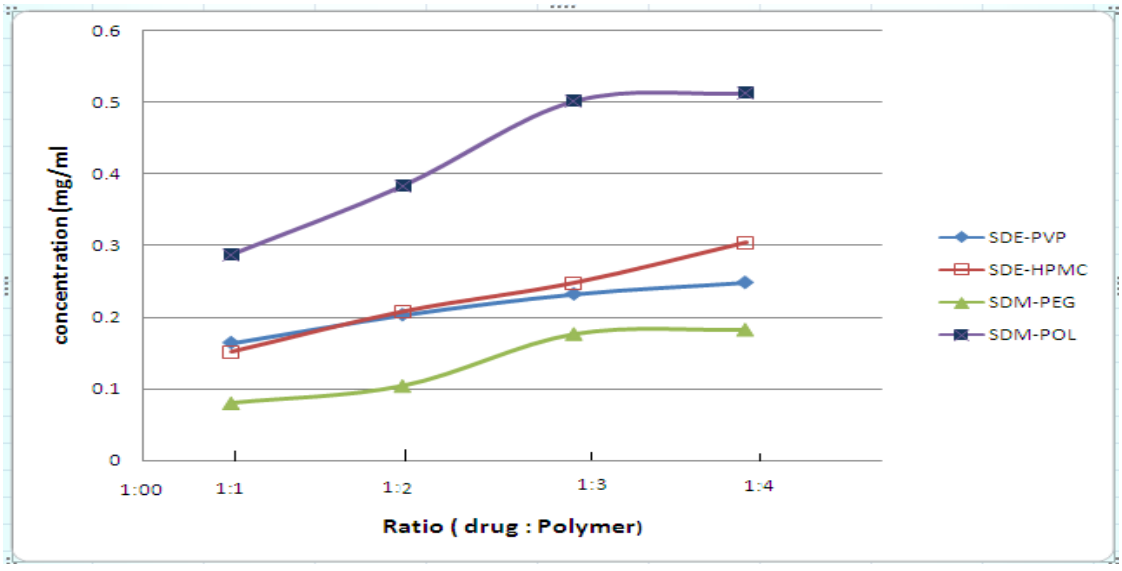

Fig.–1 -Effect of hydrophilic carriers on solubility of celecoxib in solid dispersion

Table -2 Solubility of celecoxib in polymeric combination based solid dispersion(SD)

S. NO	SD with poloxamer and PVP	SD with poloxamer and HPMC	SD with poloxamer and PEG	SD with Poloxamer and HPMC/PVP
1	0.472	0.528	0.351	0.546
2	0.464	0.536	0.318	0.556
3	0.468	0.539	0.36	0.559
4	0.452	0.545	0.363	0.561

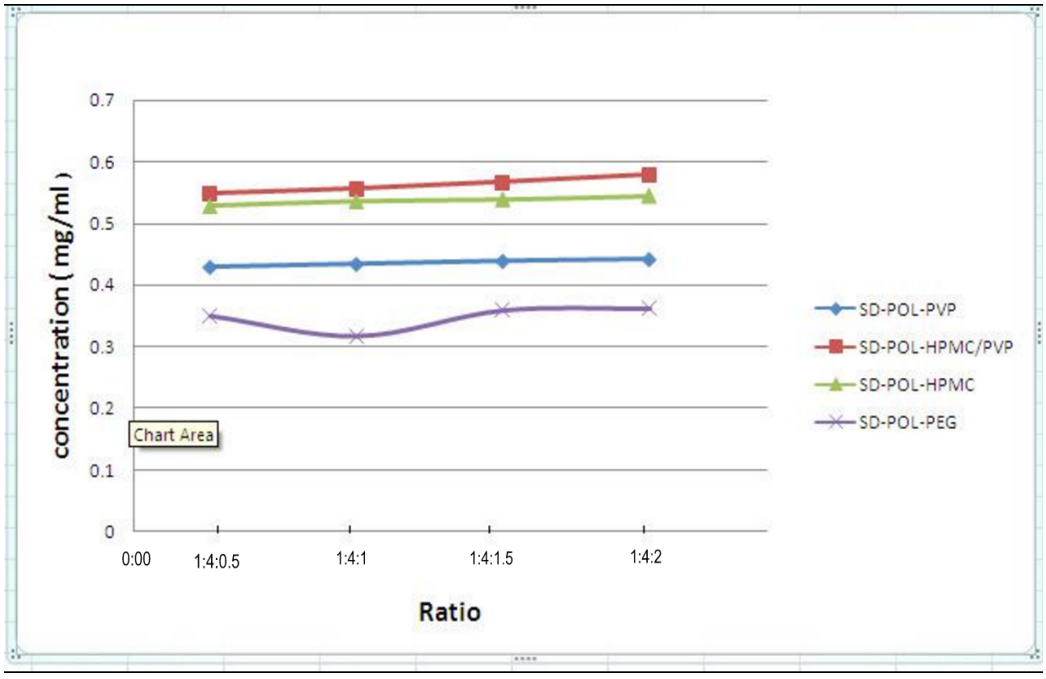

Fig.-2- Solubility effect of drug in polymeric combination based solid dispersion

Table 3- Optimization of polymeric combination of solid dispersion of drug

SN	Solid dispersion	Drug	Poloxamer 407	Polymer mixture (hpmc-pvpk30)			Solubility (mg/ml)
1	SD-F1	1	4	2	100 %	0%	0.529
2	SD-F2	1	4	2	90%	10%	0.524
3	SD-F3	1	4	2	80%	20%	0.516
4	SD-F4	1	4	2	70%	30%	0.569
5	SD-F5	1	4	2	60%	40%	0.564
6	SD-F6	1	4	2	50%	50%	0.562
7	SD-F7	1	4	2	40%	60%	0.511
8	SD-F8	1	4	2	30%	70%	0.481
9	SD-F9	1	4	2	20%	80%	0.477
10	SD-F10	1	4	2	10%	90%	0.464
11	SD-F11	1	4	2	0%	100%	0.472

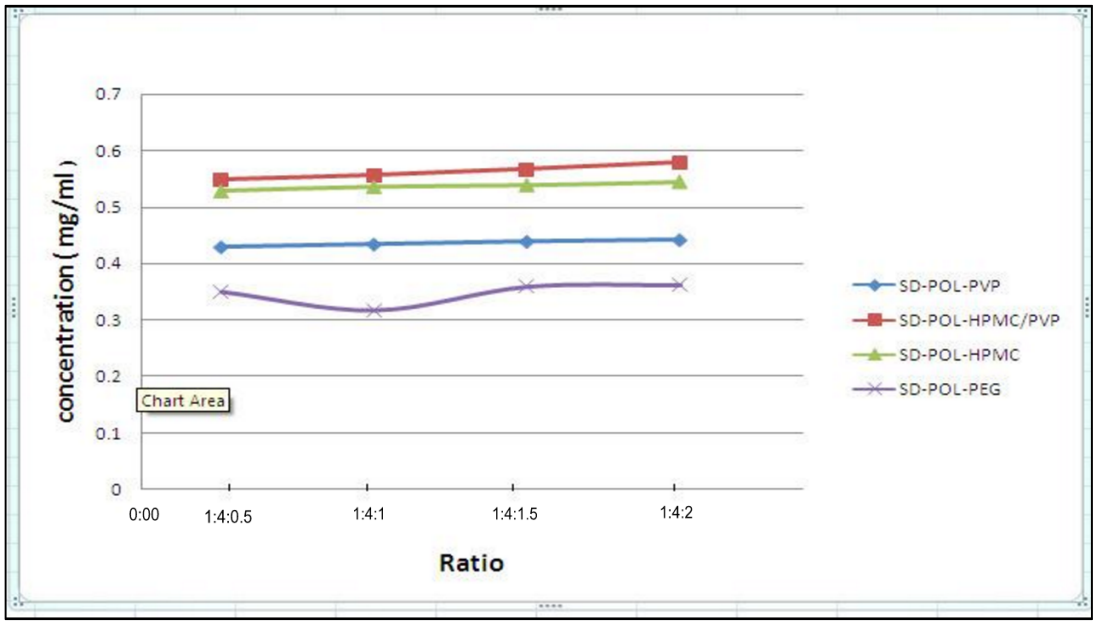

Fig.-3- Solubility effect of drug in polymeric combination based solid dispersion

Characterization of solid dispersion

The optimized batches of solid dispersion of drug with mixture of poloxamer-407, PVP-K30, and HPMC was characterized by FT-IR studies, SEM studies, differential scanning calorimetry content uniformity, and *in-vitro* release study.

Solubility studies:

Solubility studies were performed on pure drug, physical mixture, and solid dispersion analyzed by UV-spectroscopy at λmax 251nm. Increase in the absorbance reflects the increase in the solubility in terms of concentration.[13.14]

The solubility of celecoxib in solid dispersion using various hydrophilic carriers was estimate on the basis of maximum absorbance and respective concentration. Poloxamer 407 showed maximum solubility of celecoxib with increasing its concentration ratio in solid dispersion as compare to other carriers such as PVP-K30, HPMC and PEG. The solubility of pure celecoxib in water was found to 0.008 mg/ml. poloxamer 407was most effective to form a superior solid dispersion of celecoxib having significantly enhanced solubility. Particularly, solid dispersion of celecoxib with poloxamer 407 in the weight ratio of 1:4 prepared by melting solvent method enhanced the solubility of celecoxib to the greatest extent.

Poloxamer 407 based solid dispersion showed 65 times higher (0.513 mg/ml) solubility then pure celecoxib whereas solid dispersion of celecoxib with PVP, HPMC and PEG were showed 31 times (0.248mg/ml), 38 times (0.304mg/ml) and 23.5 times (0.182mg/ml) higher solubility than pure celecoxib, respectively However, it exhibited poor physical stability and due to hygroscopic nature of poloxamer 407, solid dispersion showed 10% drug degradation on 45days storage. To avoid this instability of poloxamer based solid dispersion, HPMC, PEG-8000, PVP-K30 and their combination were incorporated as an adsorbent of hygroscopic nature and inhibitor the recrystallization of drug. (Table7.12) The formulation SD-F4 showed maximum solubility 0.589mg/ml in the ratio (1:4:2) of drug, poloxamer and combination of HPMC (70%)/PVP (30%).

Infrared (IR) studies:

Infrared (IR) studies of optimized batch were carried out. The principal IR peaks of pure celecoxib IR spectra of celecoxib showed characteristic peaks at3341.51 (-NH str., primary amine), 1164.58 and 1347.75 cm^{-1} (S=O asymmetric and symmetric str., respectively) and, 1274.96 and 1229.99 cm^{-1} (-CF3) Characteristic peak obtained at reported wave number are given in (table 6.2 and figure 6.1). The polymeric combination based solid dispersion of celecoxib was analyzed by using Shimadzu IR spectroscopy. There were no considerable changes in the IR peaks of solid dispersion when compared to pure celecoxib. If there is any strong interaction between drug and carrier, itoften leads to identifiable changes in the IR profile the drug. The results of IR spectra indicated the absence of any well-defined interaction between celecoxib and Polymeric carrier (poloxamer407, PVP and HPMC).

Identification of drug was carried out by its IR spectra, obtained in KBr by using Shimadzu IR spectroscopy.

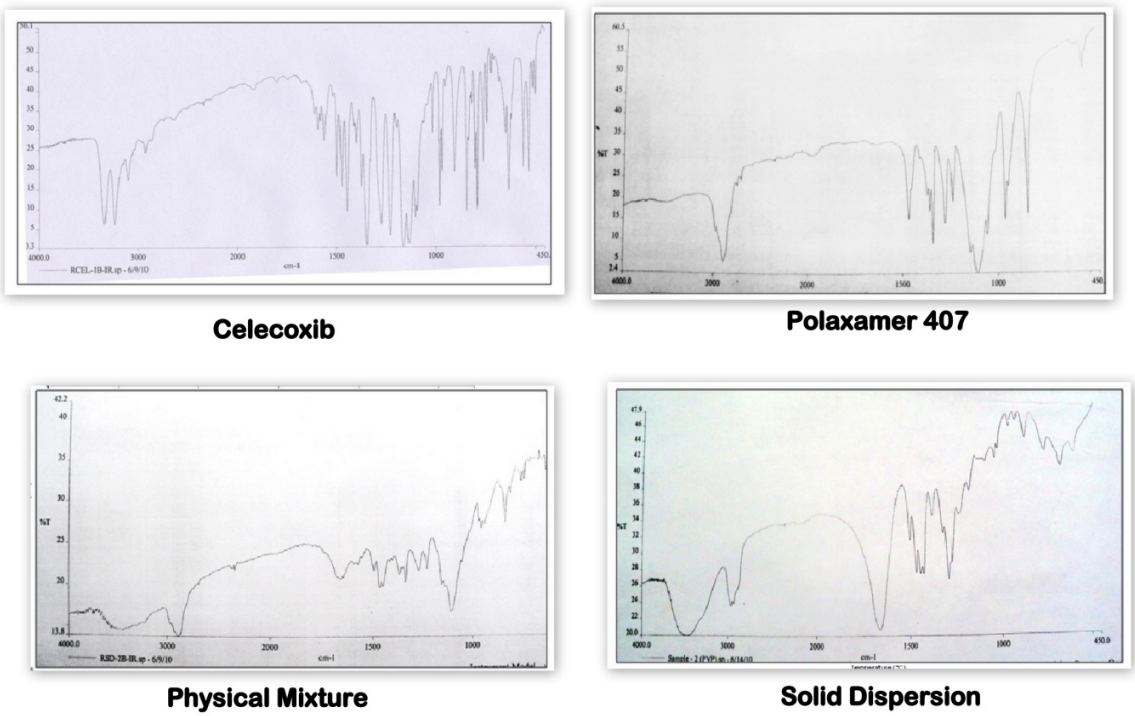

Fig.-4 - IR spectra of celecoxib, Polaxamer 407, Physical mixture & solid dispersion

Differential scanning calorimetery (DSC) analysis

The celecoxib, poloxamer-407, PVP-K30, HPMC and solid dispersion (SD-F4) were subjected to differential scanning calorimetery (DSC) analysis. DSC curves obtained for celecoxib, poloxamer-407, PVP-K30 and HPMC are displayed in chapter 6. The DSC spectrum of the celecoxib shows a sharp endothermic peak at 160.79–164.64 ◦C,with heating enthalpy(ΔH)91.25 J/g /kg. The DSC curve of poloxamer 407shows an endothermic peak near 58.34˚C with heating enthalpy(ΔH)28.450 J/g.The DSC curve of PVP-K30 and HPMC was shows 93.34◦C, with enthalpy of fusion (ΔH)30.561J/g and a single endothermic at 93.34◦C, with enthalpy (ΔH)of fusion 29.028 J/grespectively.In the DSC curve ofsolid dispersion, disappearance of the thermal features of the drug indicated that the drug has been mixed with polymer at molecular level by melting solvent method. There isno change in endothermic peaks of celecoxib in solid dispersion were observed, which confirms the no interaction between drug and excipients.

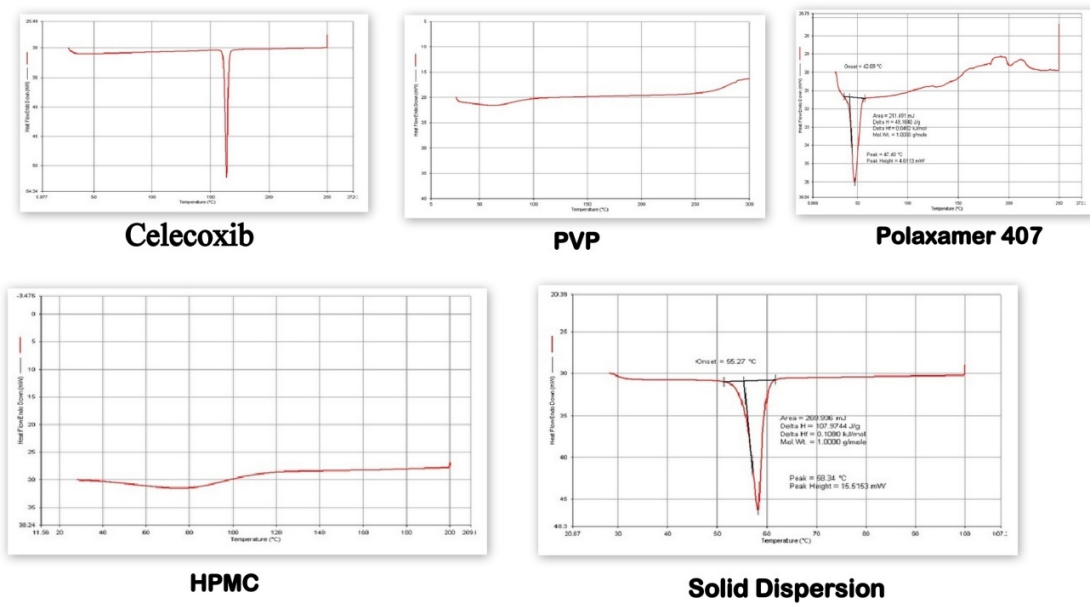

Fig.-5 - DSC curve of celecoxib, Polaxamer 407, PVP, HPMC & solid dispersion

Scanning electron microscopy (SEM)

The surface morphology of pure celecoxib, physical mixture and solid dispersion were determined by scanning electron microscopy. Pure drug shown irregular rod shaped crystalline structure whereas solid dispersion existed as popcorn crystals, the solid dispersions appeared in the form of irregular particles in which the original morphology of all components similar and tiny aggregates of amorphous pieces of irregular size were present. Therefore, the reduced particle size, increased surface area, and the close contact between the hydrophilic carriers and celecoxib might be responsible for the enhanced drug solubility found for the solid dispersion particles

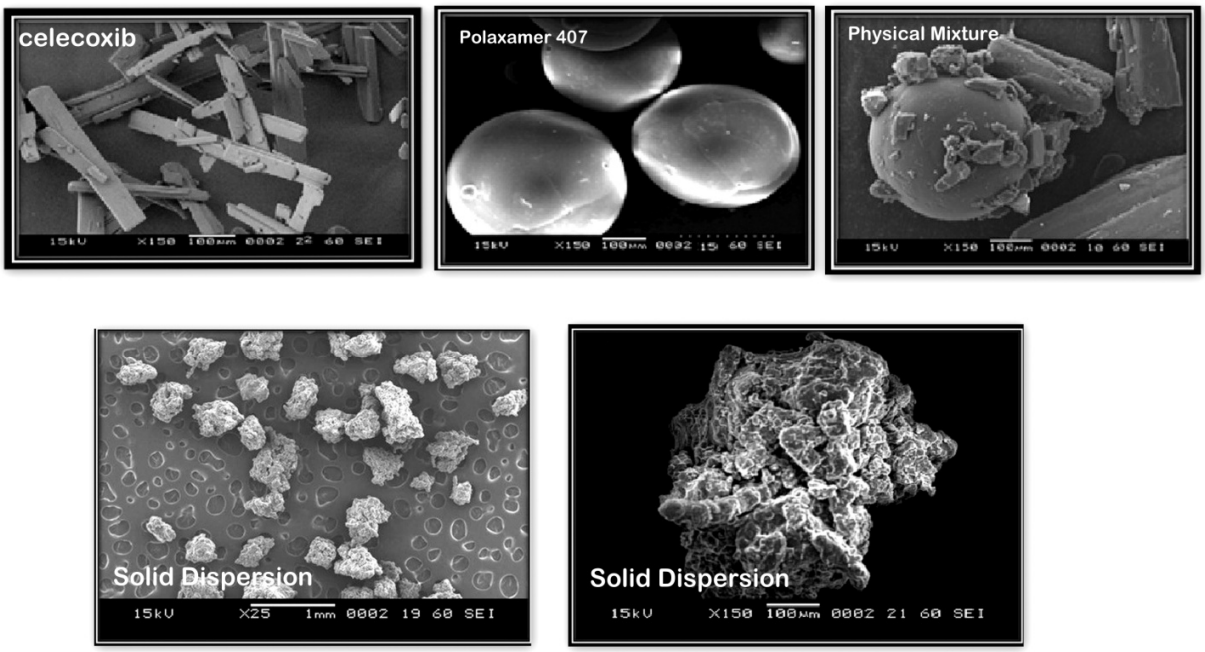

Fig.-6 - SEM image of celecoxib, Polaxamer 407, Physical Mixture & solid dispersion

Content uniformity

Content of celecoxib in solid dispersion (SD-F4, SD-F5 and SD-F1) were estimated by UV-spectrophotometric method using SHIMADZU 1700 spectrophotometer and % drug content of formulations SD-F4, SD-F5 and SD-F1 was found to be 99.07±0.13, 99.3±0.42 and 98.08±0.11 respectively.

In-vitro drug release studies

The maximum cumulative % drug release in phosphate buffer pH 6.8containing0.5% of Tween 80 for SD-F4 and SD-F5 batch was 102.47 %and 96.79 % respectively (Table.7.13, and Fig. 7.8). The maximum cumulative % drug release of pure drug was found 9.33%. In the *in-vitro* drug release studies of solid dispersion and marketed formulation were performed. In which the maximum cumulative % drug release in phosphate buffer pH 6.8containing0.5% of Tween 80for SD-F4, MF-1and MF-2 were found to be 101.59%, 88.29 %and 86.58%respectively (Table.7.14, and Fig. 7.9).

Stability Studies

The stability studies were performed on the optimized batches of solid dispersion SDM-POL-4, and SD-F4. Solid dispersion were kept on three different temperatures (4-8°C, RT, 45°C) in presence / absence of light upto 45 days. The effects of different storage condition were studied on the colour and drug content of optimized batches at regular time intervals. It was observed that formulation kept on higher temperature 45°C showed slight change in colour after 45 days. There was no significant effect of presence/absence of light on observed at room temperature.

Based on results obtained in stability study of formulations SD-F4 on different condition, it can be concluded that formulations are stable between the temperature range 4 to 45°C in both light and dark condition.

Conclusion

Summarizing the above, present study has resultedin the development of the stable solid dispersion formulation of celecoxib with poloxamer 407 and HPMC/PVP combination prepared by melting solvent method. The results of DSC and SEM studies showed that celecoxib in solid dispersions exist in the amorphous state. HPMC adsorbs the hygroscopic nature of poloxamer, gave good flowability and rapid drying property during manufacturing process of solid dispersion and PVP-K30 used as inhibitor of crystallization of drug in solid dispersion also provides good physical appearance.There was no significant effect of presence/absence of light on observed atdifferent temperatures (4-8°C, RT, 45°C) on 45 days storage.

The significant enhancement in aqueous solubility of celecoxib achieved by solid dispersion technique opens up the possibility of development of oral dosage form with improved bioavailability employing the technique. Further, the study also emphasize the need for accelerated stability studies and *in vivo* studies solid dispersion on a novel approach for enhancing the bioavailability of celecoxib in oral dosage form.

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