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RESEARCH ARTICLE

NATURAL POLYMER VIS A VIS SYNTHETIC POLYMER FOR SOLUBILITY ENHANCEMENT OF SIMVASTATIN

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ABSTRACT
The enhancement of the oral bioavailability is currently one of the greatest challenges in the development of poorly water soluble drugs. The main objective of work to enhance solubility of Simvastatin (SIM) by use of natural polymer, chitosan (CHI) and Hydroxy propyl methyl cellulose E3LV (HPMCE3LV), synthetic polymer to produce cost effective formulation. Physical mixture, co-grinding method, spray drying method are compared for solubility enhancement of simvastatin. It is found that co-grinding method is best for solubility enhancement of simvastatin.Co-grinding method applied for preparation of drug polymer complex and compared with the solubility and dissolution of marketed preparation.
Keywords: Chitosan, Cogrinding, Hydroxy propyl methyl cellulose E3LV, Simvastatin.

INTRODUCTION

The rate of dissolution of a solid is a function of its solubility that influences the absorption of relatively insoluble drugs[1]. In general, it can be stated that the rate of absorption and hence the onset of action is determined by the dissolution of the drug and subsequent transport over the intestinal membrane and passage through the liver. According to the Biopharmaceutical Classification System (BCS), four different types of drug absorption regimes are distinguished[2]. SIM is class II drug[14]. Solubility is generally expressed as the number of grams of solute in one litre of saturated solution [3.] The solute molecule is pulled into solution when the force overcomes the attractive force between the solute molecule and its neighboring solute molecule[4]. The positive ion of the solute is attracted to the negative end of the solvent molecule [5]. As the particle size reduces the surface area of the solute particle increases and the solute dissolves more rapidly [6]. pH of the medium also effect solubility of weak acidic and basic drugs[7]. The amorphous form of a compound is always more soluble than a corresponding crystal form [8]. Very weakly acidic or basic drugs may require a pH that could fall outside the accepted tolerable physiological range or may cause stability problems with formulation ingredients [9]. If a drug is poorly soluble, then it will only slowly dissolve, perhaps leading to incomplete absorption [10, 11]. Poor aqueous solubility leads to poor dissolution and ultimately poor oral bioavailability [12,23].Many methods such as particle size reduction, solid-dispersion, salt formation have mainly used for solubility, dissolution and bioavailability enhancement of poorly aqueous soluble drugs. All these techniques have some limitations [13,20]. The Particle size reduction method produces small particles having larger surface area so enhance absorption and dissolution but the small particles having limitation for wettability and flow properties [15]. Solid dispersion method having limitation because the method of preparation is tough [16, 17], change in the physicochemical property of materials which is not reproducible [18]; large scale manufacturing processes and dosage form development is very difficult [19,24]. So, Physical mixture method, co-grinding method, spray drying method were compared for solubility enhancement of simvastatin as these methods requires less money. Here the natural polymer CHI compared with synthetic polymer HPMCE3LV for solubility enhancementment of SIM to provide cost effective formulation.

MATERIAL AND METHOD

Material

Drug Simvastatin ,Chitosan(CHI) were procured from Artimis biotech, Hyderabad . Hydroxy propyl methyl cellulose (HPMCE3LV) was procured from Colorcon Asia Ltd., Goa. All other chemicals used were of analytical grade.

Drug – Excipient interaction study

The pure drug (SIM), a mixtures of SIM with HPMCE3LV and SIM with chitosan(CHI) are mixed separately with IR grade KBr in the ratio of 100:1. The pellets were then scanned over a wave range of 4000-400cm^{-1} in FTIR instrument.

Preparation of physical mixture[21]

Physical mixture of drug and polymers were prepared in different ratio such as 1:1 to 1:9 w/w. Simply polymer and drug were taken in polyethylene bag and bag was thoroughly vibrated by hand for proper mixing[21].

Preparation of co-grinding mixture [22]

Co-grinded mixture of drug and polymers were prepared in different ratio such as 1:1 to 1:9 w/w. It was co-grinded for 5min, in ceramic mortar and sieved through 100 # mesh.

Co-solvent evaporation method -Spray drying [21]

The solvent evaporation of SIM with Chitosan solution in ratio (1:1, 1:2, 1:6, 1:9 w/w) was carried out by using spray dryer (LU-222, Advanced, Labultima, India). The solutions prepare by dissolving 1g of drug in 40 ml of methanol and 1g of Chitosan in 1% acetic acid and mixed both solutions which produces clear solution. The solvent evaporated at inlet 120 ^{o}C and outlet 80 ^{o}C , feed pump speed 10 ml per minute and aspiration 45 %.

The solvent evaporation of SIM with HPMCE3LVsolution in ratio (1:1, 1:2, 1:6, 1:9 w/w) was carried out by using spray dryer (LU-222, Advanced, Labultima, India). The solutions prepare by dissolving 1g of drug in 70 ml of methanol and 1g of HPMCE3LVin 30 ml of distilled water and mixed both solutions which produces clear solution. The solvent evaporated at inlet 120^{o}C and outlet 80^{o}C, feed pump speed 10 ml per minute and aspiration 45 %.

Solubility study

The solubility was determined in pH 1.2 HCl buffer, and 7 pH buffer. The solubility of drug, and mixture were determined by taking an excess amount 30 mg of drug and added them in 10 ml of above solvents, in teflon facing screw capped vials. The samples were kept at equilibrium for a period of 48 hr on orbital shaking incubator at 37 ± 0.5^{o}C and 50 rpm. The content of vials were filtered through 0.2 micron filter, and analyzed by UV-Visible spectrophotometer at 238 nm.

Differential Scanning Calorimetry (DSC)

Analysis of samples was carried out on DSC instruments at heating rate of 10 ^{0}C /min. The measurements were performed at a heating range of 10 to 350 ^{0}C under nitrogen pressure.

X-Ray Diffraction studies (XRD)

X-ray diffraction patterns of samples were obtained using Philips diffractometer and Cu-Kα line as a source of radiation which was operated at the voltage 40 kV and the current 30 mA.

Scanning Electron Microscopy (SEM)

The morphology of samples was determined using scanning electron microscope (SEM).

Preparation of immediate release tablet

All co-grinded mixtures equivalent to 10 mg of SIM was mixed with excipients for 10 minutes in porcelain mortar, passed through 60 # sieve. This blend was mixed with magnesium stearate for 5 minutes and processed for direct compression by using 7mm round flat - faced punch of rotary tablet machine (Rimek mini press-1).

Table 1: Content of immediate release tablets (CGSCHI) cogrinding mixtures

Component in mg	F1	F2	F3	F4
Simvastatin	10	10	10	10
Chitosan	70	70	70	70
Sodium Starch glycolate	7.5	7.5	9	9
Citric acid	6	7	7	8
Sodium Bicarbonate	30	35	35	40
Lactose	23.5	17.5	16	10
Talc	1.5	1.5	1.5	1.5
Mg-stearate	1.5	1.5	1.5	1.5

Table 2: Content of immediate release tablets (CGSHPMC) co-grinding mixtures

Component in mg	F1	F2	F3	F4
Simvastatin	10	10	10	10
HPMCE3LV	60	60	60	60
Sodium Starch glycolate	6	6	7.5	7.5
Citric acid	5	6	6	7
Sodium Bicarbonate	25	30	30	35
Lactose	41	34	32.5	26.5
Talc	1.5	1.5	1.5	1.5
Mg-stearate	1.5	1.5	1.5	1.5

Drug content

Simvastatin content in the methanolic extract was analyzed spectrophotometrically at 238 nm, against the standard methanolic solution of simvastatin.

Dissolution Test

Dissolution test of tablets were performed using pH 1.2 HCl buffer and pH 7 buffer with USP dissolution apparatus II at 50 rpm and 37 ± 0.5 ^{0}C. Test samples (5 ml) were withdrawn at particular time interval (5, 10, 15, 20 and 30 minutes) and replaced with fresh dissolution media maintained at 37 ± 0.5 ^{0}C. The test samples were filtered and the concentration of dissolved drug was determined using UV spectrophotometer at λ_{max} 238 nm.

Stability Study

The accelerated stability study of co-grinding mixture tablet was checked for stability as per ICH guidelines at 40 ^{0}C/75% RH up to 3 months.

RESULT AND DISCUSSION

HPMC having surfactant activity [1]which reduces the contact angle and increases wetting of drug particles, thus enhance the solubilisation and dissolution of drug particles. It is reported that the swelling of polymers influences improvement of dissolution rate of poorly aqueous soluble drugs [2].So preferred less swelling and less viscosity polymers. Due to the less toxic effect, biodegradable nature and low production cost these polymers mainly used as drug carrier in Pharmaceutical industry.

Drug- Excipient Interaction

Drug-excipient interaction checked using FTIR spectrophotometer. The characteristic peaks found in SIM. These peaks also found in drug-polymer mixture, which indicates no drug-excipient interaction.

Table 3: Physical Mixing of Drug with Chitosan

Ratio	Absorbance		Solubility(mg/ml)		Native Solubility(mg/ml)		Increment	
	pH 1.2	pH 7	pH 1.2	pH 7	pH 1.2	pH 7	pH 1.2	pH 7
1:1	0.056	0.45	0.0860	0.55	0.0418	0.457	2.057	1.25
1:2	0.059	0.48	0.092	0.6	0.0418	0.457	2.200	1.363
1:3	0.067	0.54	0.1083	0.685	0.0418	0.457	2.590	1.556
1:4	0.074	0.66	0.1222	0.857	0.0418	0.457	2.923	1.947
1:5	0.086	0.68	0.1461	0.885	0.0418	0.457	3.495	2.011
1:6	**0.097**	**0.98**	**0.1643**	**1.31**	**0.0418**	**0.457**	**3.930**	**2.977**
1:7	0.076	0.63	0.1254	0.871	0.0418	0.457	3	1.90
1:8	0.049	0.59	0.072	0.81	0.0418	0.457	1.735	1.77
1:9	0.045	0.39	0.064	0.504	0.0418	0.457	1.54	1.104

Table 4: Co-grinding of Drug with Chitosan

Ratio	Absorbance		Solubility(mg/ml)		Native Solubility(mg/ml)		Increment	
	pH 1.2	pH 7	pH 1.2	pH 7	pH 1.2	pH 7	pH 1.2	pH 7
1:1	0.057	0.412	0.088	0.502	0.0418	0.4571	2.10	1.098
1:2	0.067	0.424	0.1083	0.520	0.0418	0.4571	2.59	1.13
1:3	0.089	0.449	0.1520	0.555	0.0418	0.4571	3.63	1.21
1:4	0.091	0.550	0.1536	0.7	0.0418	0.4571	3.67	1.53
1:5	0.095	0.625	0.1640	1.21	0.0418	0.4571	3.93	2.64
1:6	0.099	0.511	0.1719	0.644	0.0418	0.4571	4.11	1.40
1:7	**0.219**	**0.984**	**0.410**	**1.412**	**0.0418**	**0.4571**	**9.82**	**3.091**
1:8	0.079	0.320	0.1322	0.3714	0.0418	0.4571	3.16	0.81
1:9	0.068	0.319	0.1103	0.370	0.0418	0.4571	2.63	0.80

Table 5: Spray drying with chitosan

Ratio	Absorbance		Solubility(mg/ml)		Native solubility		Increment	
	pH1.2	pH7	pH1.2	pH7	pH1.2	pH 7	pH1.2	pH 7
1:1	0.051	0.419	0.0765	0.5134	0.041	0.457	1.830	1.123
1:2	0.054	0.445	0.082	0.5508	0.041	0.457	1.961	1.205
1:6	**0.076**	**0.831**	**0.1262**	**1.11**	**0.041**	**0.457**	**3.019**	**2.428**
1:9	0.049	0.327	0.072	0.3822	0.041	0.457	1.722	0.836

Table 6: Physical Mixing of Drug with HPMCE3LV

Ratio	Absorbance		Solubility(mg/ml)		Native Solubility(mg/ml)		Increment	
	pH 1.2	pH 7	pH 1.2	pH 7	pH 1.2	pH 7	pH 1.2	pH 7
1:1	0.061	0.395	0.096	0.478	0.0418	0.4571	2.296	1.045
1:2	0.065	0.401	0.1043	0.4871	0.0418	0.4571	2.495	1.065
1:3	0.083	0.578	0.1401	0.74	0.0418	0.4571	3.351	1.618
1:4	0.095	0.502	0.1640	0.6328	0.0418	0.4571	3.923	1.384
1:5	0.103	0.475	0.1799	0.592	0.0418	0.4571	4.303	1.295
1:6	**0.121**	**0.893**	**0.2157**	**1.273**	**0.0418**	**0.4571**	**5.160**	**2.787**
1:7	0.081	0.512	0.1361	0.6457	0.0418	0.4571	3.255	1.412
1:8	0.071	0.504	0.1163	0.6342	0.0418	0.4571	2.782	1.387
1:9	0.053	0.486	0.080	0.6085	0.0418	0.4571	1.913	1.331

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Table 7: Co-grinding of Drug with HPMCE3LV

Ratio	Absorbance		Solubility(mg/ml)		Native Solubility(mg/ml)		Increment	
	pH 1.2	pH 7	pH 1.2	pH 7	pH 1.2	pH 7	pH 1.2	pH 7
1:1	0.049	0.39	0.072	0.471	0.041	0.457	1.735	1.031
1:2	0.057	0.44	0.088	0.542	0.041	0.457	2.116	1.187
1:3	0.063	0.51	0.100	0.642	0.041	0.457	2.401	1.406
1:4	0.069	0.59	0.112	0.757	0.041	0.457	2.687	1.656
1:5	0.079	0.65	0.132	0.842	0.041	0.457	3.162	1.844
1:6	0.089	0.89	0.152	1.185	0.041	0.457	3.638	2.594
1:7	0.069	0.59	0.112	0.757	0.041	0.457	2.687	1.656
1:8	0.053	0.54	0.080	0.685	0.041	0.457	1.926	1.500
1:9	0.049	0.47	0.072	0.585	0.041	0.457	1.735	1.281

Solubility data for SIM, PMSCHI (Physical mixture of SIM and CHI), CGSCHI (Co grounded mixture of SIM and CHI),SDSCHI (Spray dried mixture of SIM and CHI), in different solvents are given in Table 3,4,5. ANOVA ($P<0.001$) performed on solubility parameter demonstrated significant difference between solubility of SIM with co-grinded mixtures. Solubility data of PMSCHI, SDSCHI shows that ratio 1:6 and CGSCHI shows that ratio 1:7 shows highest solubility. Hence co-grinding mixture is optimized for further processing.

Table 8: Spray drying with HPMCE3LV

Ratio	Absorbance		Solubility(mg/ml)		Native solubility		Increment	
	pH1.2	pH7	pH1.2	pH7	pH1.2	pH 7	pH1.2	pH 7
1:1	0.049	0.361	0.072	0.4302	0.041	0.457	1.722	0.941
1:2	0.055	0.429	0.084	0.5282	0.041	0.457	2.009	1.155
1:6	**0.069**	**0.812**	**0.1123**	**1.07**	**0.041**	**0.457**	**2.686**	**2.341**
1:9	0.052	0.493	0.078	0.6122	0.041	0.457	1.866	1.339

Solubility data for SIM, PMSHPMC (Physical mixture of SIM and HPMC), CGSHPMC (Co grounded mixture of SIM and HPMC), SDSHPMC (Spray dried mixture of SIM and HPMC), in different solvents are given in Table 6,7,8. ANOVA ($P<0.001$) performed on solubility parameter demonstrated significant difference between solubility of SIM with co-grinded mixtures. Solubility data of PMSHPMC, CGSHPMC, SDSHPMC shows that ratio 1:6 shows highest solubility. Hence co-grinding mixture is optimized for further processing as it shows good solubility enhancement.

Differential Scanning Calorimetry (DSC)

Results of DSC studies are given in following figures.

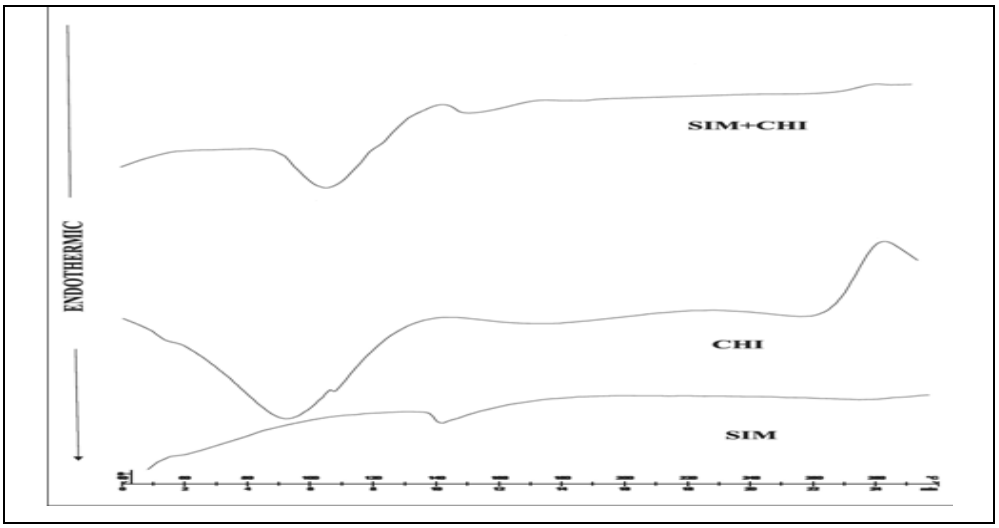

Figure 1: DSC thermogram of SIM, CHI, CGSCHI

SIM was characterised by sharp melting endothermic peak at 140.63^{0}C.CHI shows broad endothermic peak at 90.08 ^{0}C .CGSCHIshows less intensity of the peak which indicate the conversion of crystalline SIM to amorphous. SIM was characterised by sharp melting endothermic peak at 140.63 ^{0}C. HPMC shows broad endothermic peak at 71.97 ^{0}C. CGSHPMC shows less intensity of the peak which indicate the conversion of crystalline SIM to amorphous.

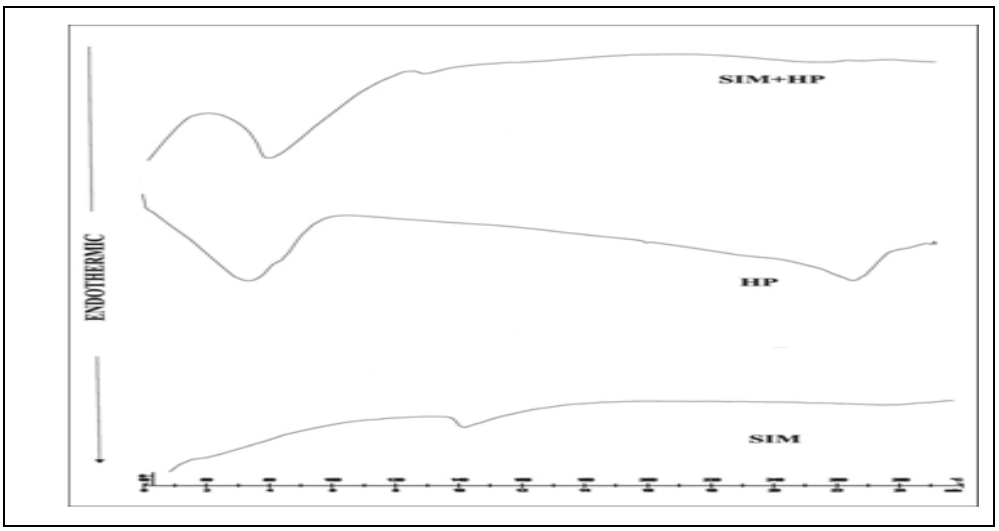

Figure 2: DSC thermogram of SIM, HPMC and CGSHPMC

X-ray Diffraction Studies (XRD)

The X-ray diffraction patterns of drug and polymers are given in following figures.

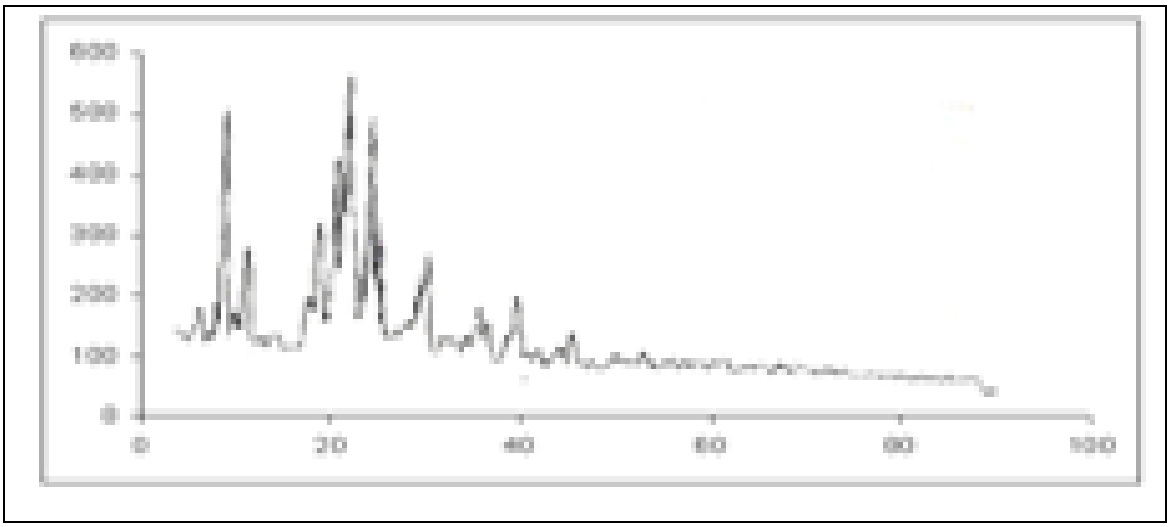

Figure 3: the **X-ray diffraction patterns of Simvastatin**

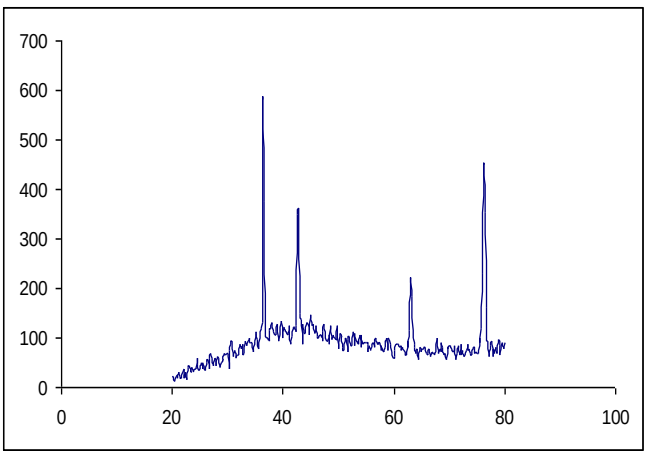

Figure 4: the **X-ray diffraction patterns of CHI**

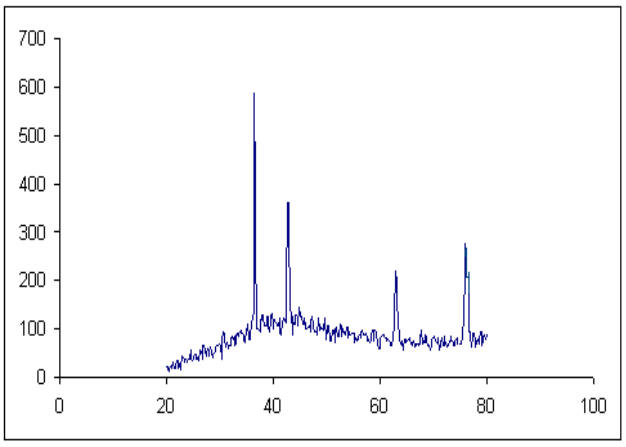

Figure 5: the **X-ray diffraction patterns of CGSCHI**

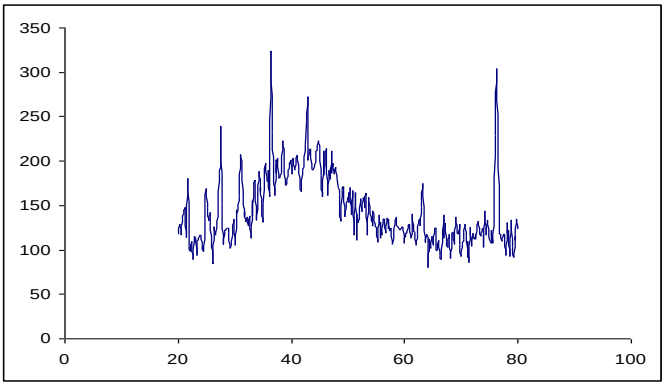

Figure 6.The X-ray diffraction patterns of HPMCE3LV

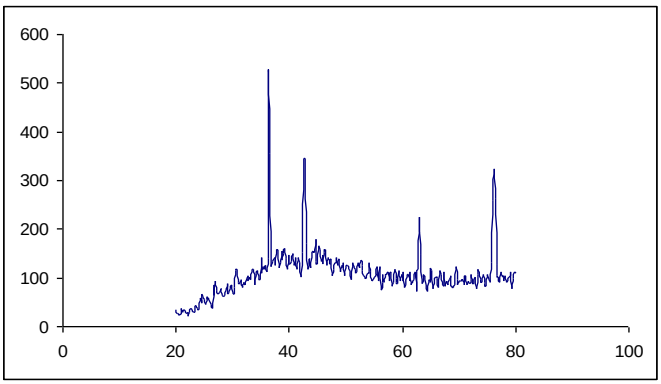

Figure 7: The X-ray diffraction patterns of CGSHPMC

The characteristic peaks in X-RD indicate the crystalline nature of SIM.X-R of CGSCHI, CGSHPMC shows absence of some characteristic peaks of SIM. Intensity of peaks in co-grinded indicates conversion of crystalline to amorphous.

Scanning Electron Microscopy (SEM)

The morphological characteristic of drug and processed drug polymer complex was shown in following figures.

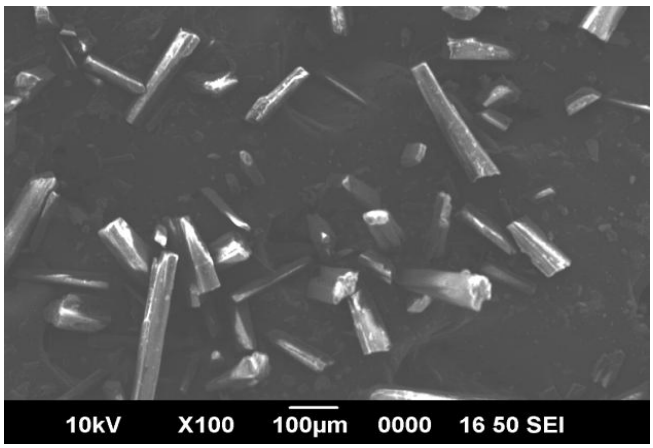

Figure 8: SEM of SIM

This data further conformed by morphological characterisation of SIM, CHI, CGSCHI HPMCE3LV, CGSHPMC. SIM particles appeared as plate like crystals (100µm) with smooth surfaces where as chitosan appeared as flake like particles, HPMC consisted of amorphous particles of rather irregular size and shape. Crystals of SIM was co-grinded with polymer, it seemed that morphology of SIM was changed in co-grinded mixtures.

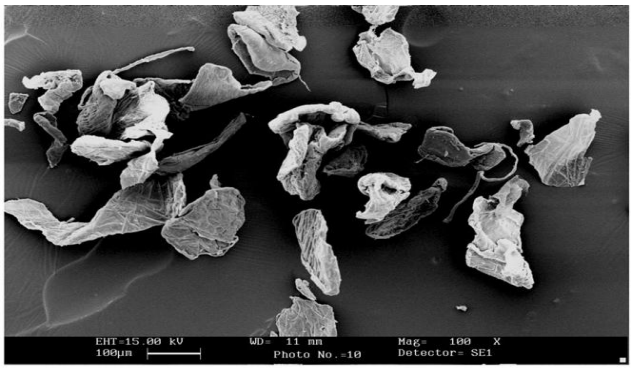

Figure 9: SEM of CHI

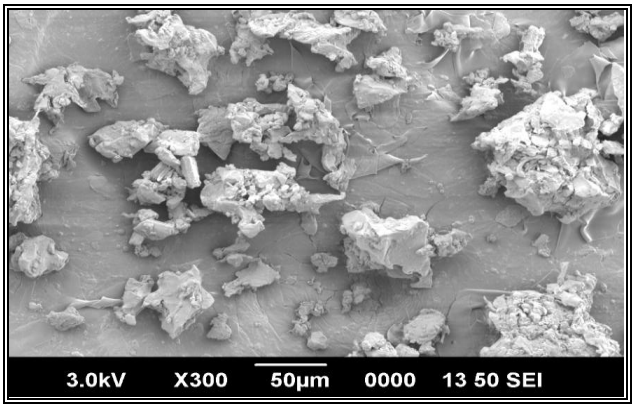

Figure 10: SEM of CGSCHI

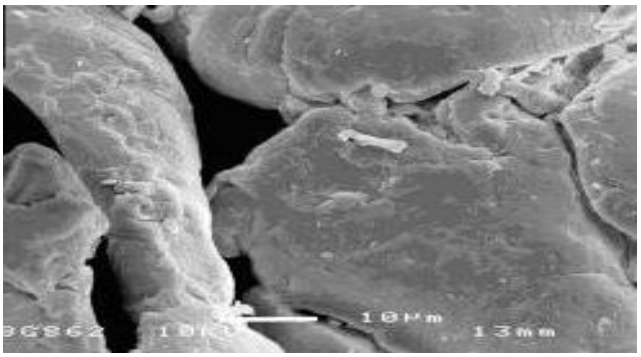

Figure 11: SEM of HPMCE3LV

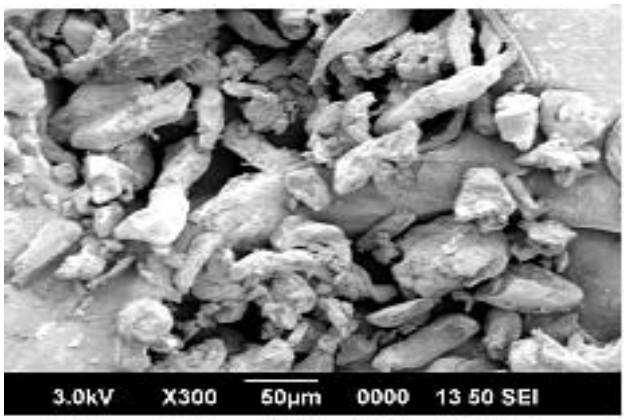

Figure 12: SEM of CGSHPMC

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Evaluation of formulation

Table 9: Pre Compression parameter of SIM-CHI immediate release tablet

Batch	Angle of Repose	LBD (g/mL)	TBD (g/mL)	Carr's Index (%)	Hausners Ratio
F1	33.23	0.52	0.64	18.40	1.23
F2	32.58	0.47	0.53	17.32	1.12
F3	31.71	0.52	0.60	19.33	1.15
F4	34.47	0.49	0.57	15.03	1.16

Table 10: Pre Compression parameter of SIM-HPMC immediate release tablet

Batch	Angle of Repose	LBD (g/mL)	TBD (g/mL)	Carr's Index (%)	Hausners Ratio
F1	35.74	0.52	0.64	17.89	1.19
F2	33.56	0.47	0.53	18.11	1.26
F3	36.24	0.52	0.60	19.50	1.30
F4	35.08	0.49	0.57	16.23	1.23

Table 11: Evaluation of SIM-CHI cogrinding Immediate release Tablet

Properties	F1	F2	F3	F4
Weight (mg) Mean ± SD	151 ± 1.3	148 ± 0.8	146 ± 0.6	149 ± 1.4
Hardness (kg/cm^2)	2- 3	2-3	2-3	2-3
Thickness (mm) Mean ± SD	1.98 ± 0.08	2.05 ± 0.07	2.12 ± .07	2.31 ± .05
Friability (%)	0.58	0.54	0.68	0.62
Drug content (%) Mean ± SD	98.6 ± 0.8	99.2 ± 1.3	102 ± 0.8	96 ± 1.4
Disintegration time (Sec)	120 ± 23	152 ± 31	102 ± 16	84 ± 23
Wetting time (seconds)	410 ± 24	340 ± 62	510 ± 27	311 ± 42

Table 12: Evaluation of SIM-HPMC cogrinding Immediate release Tablet

Properties	F1	F2	F3	F4
Weight (mg) Mean ± SD	149± 0.88	150 ± 0.67	148 ± 0.58	149 ± 1.8
Hardness (kg/cm^2)	2- 3	2-3	2-3	2-3
Thickness (mm) Mean ± SD	2.06 ± 0.07	2.09 ± 0.03	2.11 ± 0.04	2.29± 0.03
Friability (%)	0.69	0.57	0.78	0.86
Drug content (%) Mean ± SD	99.5± 0.5	100.2 ± 2.5	100 ± 1.2	98± 2.10
Disintegration time (Sec)	180 ± 28	195 ± 32	205± 25	170± 11
Wetting time (seconds)	480 ± 45	420 ± 58	510 ± 64	380 ± 54

Dissolution efficiency (DE)

The dissolution profile of tablets in 1.2 pH HCl buffer and 7 pH buffer are given in Table. The dissolution of co-grinded mixture tablets were compared to that of marketed tablet (MKT) and SIM. Dissolution efficiency was calculated by using software **PCP-Disso-v3.** ANOVA performed on the dissolution efficiency (DE) of SIM, marketed tablet. Significant difference was found between co-grinded mixture tablets (F4), marketed tablet and SIM. This indicates, the dissolution rate of SIM improved in presence of CHI,HPMC. Tablets of CGSCHI,CGSHPMC have shown better solubility and dissolution enhancement.

Table 13: DE of SIM and various cogrinded (Mean ± S.D), n= 3

Product	1.2 pH HCL buffer		7 pH buffer	
	DE_{10}	DE_{30}	DE_{10}	DE_{30}
SIM	18.12 ± 0.72	25.94± 0.38	26.22 ± 0.90	51.66 ± 0.69
MKT	24.91± 1.38	30.51± 1.02	20.94± 4.68	29.25± 0.41
CGSCHI (F1)	35.82± 0.99	57.98± 0.79	20.01± 0.99	39.00± 0.79
CGSCHI (F2)	37.90± 1.59	59.52± 1.09	20.97± 1.59	40.09± 1.09
CGSCHI (F3)	40.25± 3.64	61.89± 4.98	21.46± 3.64	41.83± 4.97
CGSCHI (F4)	**41.55± 0.52**	**64.64± 0.36**	**22.21± 1.49**	**45.92± 0.39**
CGSHPMC(F5)	34.73± 0.55	55.84± 0.98	19.67± 0.66	38.67± 1.68
CGSHPMC(F6)	36.69± 1.17	58.06± 1.22	21.49± 3.71	40.00± 2.28
CGSHPMC(F7)	39.43± 4.36	61.04±0.76	22.18± 4.36	41.04± 1.62
CGSHPMC(F8)	40.99± 4.39	63.86 ± 1.60	22.90± 0.43	45.16 ± 0.55

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Stability Study

Accelerated stability studies were performed at 40 ^{0}C/75% RH as per the ICH guidelines. Based on the results of initial characterization CGSCHI (F4), CGSHPMC (F8) are thought to be the superior formulation and hence further subjected to accelerated stability study. There was insignificant decrease in dissolution rate of SIM over the period of 3 months. Dissolution profile (DE_{30}) of optimized batches before and after stability is given in Table.

Table 14: DE_{30} of CGSCHI tablets before and after stability (mean ± S.D), n = 3.

	BEFORE STABILITY		AFTER STABILITY	
BATCH	**1.2 pH buffer**	**7 pH buffer**	**1.2 pH buffer**	**7 pH buffer**
CGSCHI (F4)	64.64± 0.36	45.92± 0.39	63.86± 0.54	46.34± 0.68
CGSHPMC(F8)	63.86± 1.60	45.16±0.55	61.08± 0.89	44.93± 0.17

CONCLUSION

The present work successfully demonstrated the use of CHI and HPMCE3LV, a low viscosity grade of HPMC polymers as solubility enhancing material. Solubility enhancing properties of CHI and HPMCE3LV were established by solubility studies and confirmed with dissolution studies. Characterization of solid mixtures of drug with polymer such as DSC, XRD and SEM studies supported the results. The crystalline state of the drug was converted successfully into amorphous state by physical mixing, co-grinding and sprays drying the drug with polymer. But co-grinding shows the best solubility enhancing capacity. CHI shows better solubility enhancement as compare to HPMCE3LV.The natural polymers having surfactant activity that enhances the solubility and dissolution rate of drug. This natural polymers having advantage over other synthetic polymeras this polymers are biocompatible, biodegradable and having low cost.

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