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Article

Optimization and Classification of Solid Dispersion of Piroxicam by Mixed Solvency Model

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I N F O

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A B S T R A C T

In this examination traditional piroxicam container has moderate beginning of activity (45-60 min) and helpless bioavailability (50-60%), and along these lines can't be given in crisis clinical circumstances like postoperative agony, rheumatoid joint inflammation or osteoarthritis. So, motivation behind research was to give a quick dissolving oral dose type of piroxicam, which can give speedy beginning of activity by utilizing blended dissolvability idea. First did at first dissolvability of piroxicam was resolved separately in 3 hydrotropic specialists like sodium benzoate, sodium citrate, niacinamide and 4 water solvent polymer in particular hydroxy propyl beta cyclodextrin, PVP K30, PEG400, PEG8000 at convergence of 40% w/v arrangements utilizing decontaminated water as dissolvable. Most elevated dissolvability was gotten in 40% sodium benzoate arrangement. At that point various mixes of 2, 3 and 4 hydrotropic agents+water dissolvable polymer in various proportions were utilized to decide dissolvability, so that all out grouping of solubilizer mix was consistently 40%. Most elevated dissolvability was gotten in arrangement of sodium benzoate+HP-BCD+PVP K30 at optimum ratio of 15:15:10. This enhanced blend was used in getting ready strong scatterings arranged by blended dissolvability idea utilizing refined water as dissolvable arranged SD perform by in vitro disintegration study and described by XRD, SEM, FTIR, DSC examination.

Keywords: Piroxicam, Solid Dispersion, Solubility, Mixed Solvency Concept

Introduction

The absorption of drugs that are poorly soluble in water is limited by their degree and rate of dissolution in organic fluids, which in turn are a function of the surface area of the solid. It is thus unsurprising that reducing particle size is the most widely used method of growing surface contact between the drug and the solvent, and hence, of improving solubility.

Sekiguchi and OBI were first proposed in 1961 Solid scatterings have been utilized in this association. These blends were accordingly concentrated in detail Chiou and Riegelman in 1970, and their turn of events and significance have been archived in a few reports of their viability.[1]

The current examination was intended to analyze the disintegration profile of strong scatterings of piroxicam in polyvinyl pirrolidone k30+sodium benzoate+hydroxyl propyl beta cyclodextrin with the disintegration profile in actual blends and in piroxicam alone, looking for potential expansions in solvency and disintegration pace of the dynamic rule. We likewise broke down the drug accessibility of the medication in containers arranged with strong scatterings. The physical-substance qualities of the strong scatterings researched were accounted for in another investigation.[2]

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Materials and Methods

Piroxicam was talented example by Meshapharma Pvt. Ltd., Mumbai. Hydroxy propyl beta cyclodextrin skilled example by Glenmark Ltd. Mumbai. sodium benzoate, sodium citrate, PEG 400, PEG 8000, PVP K30 were bought from SD fine synthetic substances, Mumbai, India. Niacinamide was bought from Morden Lab Ltd. Indore, India. Every one of the synthetics and reagents utilized were of scientific evaluation.

Initially solubility of piroxicam was determined individually in solutions of 3 hydrotropic agents (Ha) namely sodiumbenzoate (SB), sodium citrate (SC), Niacinamide (NM) and water-soluble polymer PEG 400, PEG 8000, PVP K30, and Hydroxy propyl beta cyclodextrin at concentration of 40% solutions using purified water as solvent (Table 1). For determining solubility, accurately measured 5 ml of a particular blend of hydrotropic agent was taken in a 10 ml volumetric flask also, abundance measure of medication was added and precisely shaken until soaked arrangement was framed. The volumetric cup was shaken on mechanical shaker for 12h with the goal that balance dissolvability can be accomplished, and arrangement could equilibrate for 24h. At that point arrangement was centrifuging that 2000 rpm for 5 min in ultra-axis and afterward arrangement was separated through Whatman grade 41 channel. Aliquot was reasonably weakened with decontaminated water and examined utilizing UV spectrophotometer at 358.6 nm. From the aftereffects of above examinations, it was presumed that solvency of piroxicam was expanding in hydrotropic specialists, However, most elevated dissolvability was acquired in 40% sodium benzoate arrangement.

Table 1.Equilibrium solubility of piroxicam in different water-soluble solubilizer

S.No	Solu-bilizers	Concent-ration (%w/v)	Solubility (%w/v)	Solubility enhance-ment ratio
1.	Distilled water	-	0.007	-
2.	SB	40	1.709	244.14
3.	SC	40	0.115	16.42
4.	NM	40	0.670	95.71
5.	HP-BCD	40	0.561	80.11
6.	PEG 400	40	0.057	8.14
7.	PEG 8000	40	0.059	8.42
8.	PVP K 30	40	0.057	8.14

At that point various blends of previously mentioned hydrotropic specialists and water-dissolvable polymer in various proportions were attempted to decide improvement in solvency, so that all out centralization of solubilizers was consistently 40% w/v (Tables 2-5). The solubilizer mix SB+HP-BCD+PVP K30 in the proportion of 15:15:10 gave the most noteworthy dissolvability upgrade, and consequently, this advanced mix was chosen for the readiness of strong scatterings.

Table 2.Equilibrium solubility of piroxicam in different blends of two water soluble solubilizers

S. No	Blends of solu-bilizers	Total Conc. (%w/v)	Ratio	Solu-bility (%w/v)	Solubility enhanc-ement ratio
1.	SB+PVP	40	20:20	0.807	115.28
2.	SB+PEG 8000	40	20:20	0.699	99.85
3.	SB+NM	40	20:20	1.405	200.71
4.	SB+SC	40	20:20	0.650	92.85
5.	SB+HP-BCD	40	20:20	0.989	141.27
6.	NM+HP-BCD	40	20:20	0.870	124.28

Table 3.Equilibrium solubility of piroxicam in different blends of three water soluble solubilizers

S. No	Blends of solu-bilizers	Total Conc. (%w /v)	Ratio	Solu-bility (%w/v)	Solu-bility enhan cement ratio
1.	SB+PEG 400+PVP	40	13.4+13.3 +13.3	1.505	215.10
2.	SB+PEG 8000+PVP	40	13.4+13.3 +13.3	1.535	219.28
3.	SB+HP-BCD +PVP	40	13.4+13.3 +13.3	1.725	246.42
4.	SB+NM+SC	40	13.4+13.3 +13.3	1.110	158.57
5.	NM+HP-BCD +PVP	40	13.4+13.3 +13.3	1.274	182.01
6.	NM+PEG 8000+PVP	40	13.4+13.3 +13.3	0.910	130.00

Preparation of solid Dispersions of Piroxicam by Application of Mixed-solvency concept

For arrangement of strong scattering in1:4 proportion (drug: solubilisers mix) precisely weighed 1.5 gm. sodium benzoate, 1.5gm. HP-BCD and 1 gm. PVP K 30 were taken in a 100 ml measuring utensil and were blended appropriately.

Table 4.Equilibrium solubility of piroxicam in different blends of four water soluble solubilizers

S. No	Blends of solubilizers	Total Conc. (%w/v)	Ratio	Solubility (%w/v)	Solubility enhancement ratio
1.	SB+PEG400+PVP+NM	40	10:10:10:10	0.923	131.85
2.	SB+PEG8000+PVP+NM	40	10:10:10:10	0.987	141.00
3.	SB+HP-BCD+PVP+NM	40	10:10:10:10	1.163	166.14
4.	SB+NM+SC+HP-BCD	40	10:10:10:10	0.945	135.12

Table 5.Equilibrium solubility of piroxicam in different Ratio of (SB+HPBCD+PVP K30) water soluble solubilizers

S. No	Blends of solubilizers	Total Conc. (%w/v)	Ratio	Solubility (%w/v)	Solubility enhancement ratio
1.	SB+HP-BCD+PVP	40	15:10:15	1.255	179.28
2.	SB+HP-BCD+PVP	40	15:15:10	1.748	249.71
3.	SB+HP-BCD+PVP	40	10:15:15	1.187	169.57
4.	SB+HP-BCD+PVP	40	15:20:05	1.680	240.00
5.	SB+HP-BCD+PVP	40	20:15:05	1.617	231.10

At that point least conceivable amount of warm, refined water adequate to break up the above combination was added, in light of the fact that lesser the measure of water lesser will be the time needed to vanish it and compound soundness of medication may not be influenced adversely(during expulsion of water) Dissolution of the water-soluble additives (solubilizers) mixture was facilitated by agitation of a teflon coated magnetic rice bead on a high-speed magnetic stirrer. After complete dissolution of solubilizers, 1 gm. of piroxicam was dissolved in the above solution and temperature was maintained in the range of 55-60ºC to facilitate the evaporation of water. As evaporation proceeded, speed of rice bead automatically decreased and it stopped stirring when most of the water was evaporated, thus indicating the formation of solid dispersion (wet).

The wet solid dispersion, in this way, acquired was spread on a few glass petri plates and these Petri plates were kept in hot air-dry stove kept up at 50±2ºC so that excess dampness could likewise be dissipated effectively and a consistent load with no further weight reduction (because of vanishing) could be gotten. After complete drying, strong scatterings were squashed utilizing a glass mortar pestle and went through strainer #40 and were at long last put away in a water/air proof glass bottle. Same method was used to get ready strong scattering in the proportion of 1:6, 1:8, 1:10 and 1:12 utilizing fitting amount of solubilizers. Amount taken in readiness of strong scattering appeared in Table 6.

Table 6. Composition of solid dispersion

S. No.	Drug: Solu-bilizres ratio	Quantity taken in gm			
		Pirox-icam (gm)	Sodium benzoate (gm)	HP-BCD (gm)	PVP K 30 (gm)
1.	1:4	1.00	1.50	1.50	1.00
2.	1:6	1.00	2.25	2.25	1.50
3.	1:8	1.00	3.00	3.00	2.00
4.	1:10	1.00	3.75	3.75	2.50
5.	1:12	1.00	4.50	4.50	3.00

In Vitro Dissolution Rate Studies

Dissolution tests are one of the most widely used tests in quality control of dosage forms. Dissolution tests become especially important when dissolution is the rate limiting step as in the case of B.C.S. class II or B.C.S. class IV drugs. To select the optimum ratio of solid dispersion, physical mixture, plain drug and final formulation, dissolution rate studies were performed.

Procedure as per B.P

Solid dispersion or physical mixture comparable to 20 mg of piroxicam were tried in disintegration rate considers utilizing USP type II disintegration test contraption (Model TDT 08L, Electrolab Mumbai, India) with oar to pivot at 100 rpm. 900 ml of 0.1MHCl was taken as disintegration media with

temperature of 37+ 0.5°C. At unmistakable time stretches 10 ml of the examples were removed and were investigated for drug content. Removed examples were likewise supplanted with new disintegration media. Computations for drug were finished utilizing particular relapse conditions and the consequences of the disintegration study was appeared in Table 7-9 and graphically address in Graph 1-3.

Table 7.Comparative account of dissolution profiles of physical mixture containing different drug: solubilizers ratio

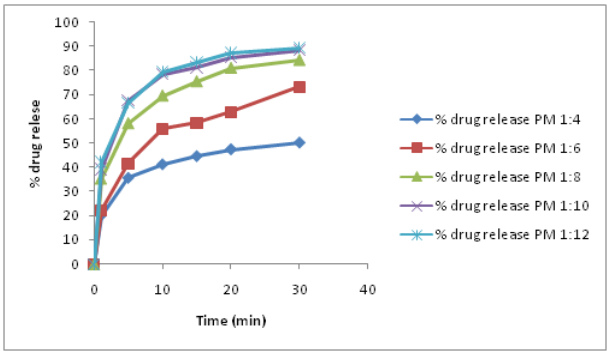
S. No	Time (min)	% Drug release of physical mixture				
		1:4	1:6	1:8	1:10	1:12
1.	1	20.04	22.33	35.45	39.13	42.17
2.	5	35.58	41.67	58.34	67.70	66.58
3.	10	41.15	55.94	69.77	78.54	79.45
4.	15	44.52	58.49	75.66	81.25	83.34
5.	20	47.35	62.84	81.25	85.34	87.17
6.	30	50.11	73.22	84.51	88.32	89.25

Table 8.Comparative account of dissolution profiles of solid dispersions containing different drug: solubilizers ratio

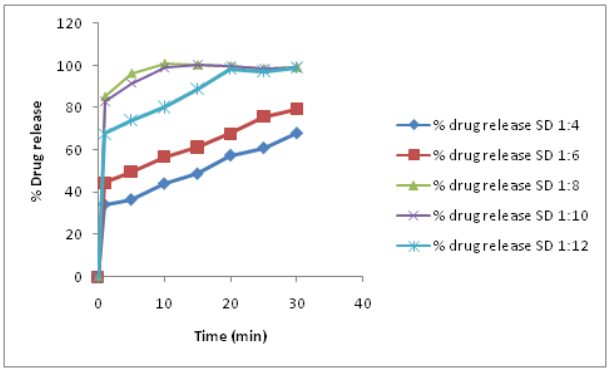
S. No	Time (min)	% Drug release of solid dispersion				
		1:4	1:6	1:8	1:10	1:12
1.	1	34.13	44.55	85.09	82.77	67.72
2.	5	36.44	49.76	96.10	91.46	74.09
3.	10	43.97	56.71	100.73	98.99	80.46
4.	15	48.61	61.35	100.15	100.15	89.15
5.	20	57.29	67.72	99.57	100.15	98.41
6.	25	60.77	75.83	-	-	-
7.	30	67.72	79.30	-	-	-
8.	45	78.14	86.83	-	-	-

Table 9.Comparative account of dissolution profiles of piroxicam pure drug, physical mixture, solid dispersion

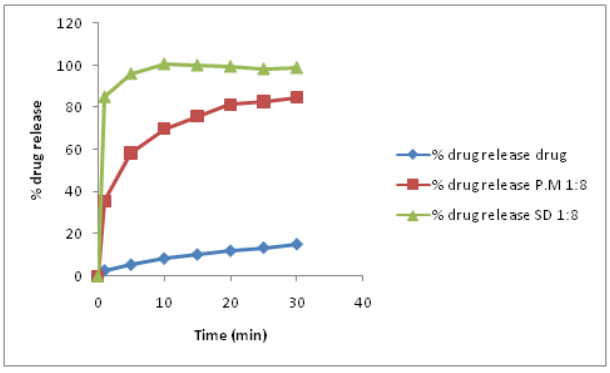
S. No.	Time (min)	% Drug release		
		Pure drug	PM 1:8	SD 1:8
1.	1	2.66	35.45	85.09
2.	5	5.38	58.34	96.10
3.	10	8.27	69.77	100.73
4.	15	10.18	75.66	100.15
5.	20	11.92	81.25	99.57
6.	25	13.37	82.48	98.41
7.	30	14.99	84.51	98.99



Graph 1.Comparative account of dissolution profiles of physical mixture



Graph 2.Comparative account of dissolution profiles of solid dispersions



Graph 3.Comparative account of dissolution profiles of pure drug, physical mixture 1:8, solid dispersions 1:8.

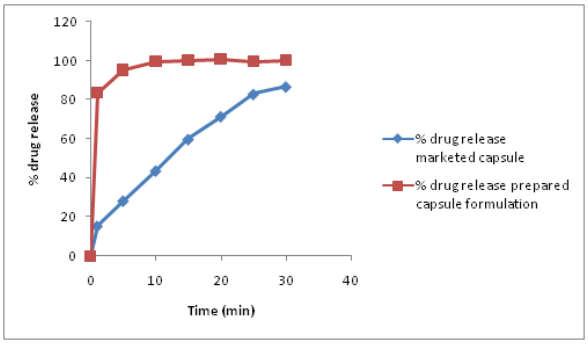
After perform SD dissolution study, optimised solid dispersion filled in hard gelatin capsule and performed dissolution study of these prepared capsule, and compare with marketed capsule. Result shown in Table 10 and graphically represent in Graph 4.

Micromeritic Properties

Micromeritic properties of the solid dispersions studied were bulk density, tapped density, compressibility index, Hausner ratio and angle of repose. The results are reported in Table 11.

Table 10.Comparative account of dissolution profiles of piroxicam marketed capsule and prepared capsule formulation

S. No.	Time (min)	% drug release	
		Marketed capsule	Prepared Capsule formulation
1.	5	15.17	83.51
2.	10	28.12	95.24
3.	15	43.51	99.57
4.	20	59.64	100.15
5.	25	71.35	100.74
6.	30	82.76	99.57
7.	35	86.58	-



Graph 4.Comparative account of dissolution profiles of piroxicam marketed capsule and prepared capsule formulation

Table 11.Micromeretic properties of solid dispersion of piroxicam

S.No.	Parameter	Observation	Inference
1	Angle of repose	$34^0 01'$	Good flow
2	Tap density	0.868gm/ml	-
3	Bulk density	0.735gm/ml	-
4	Carr's index	15.32	Fair flow
5	Hausner's ratio	0.933	Good flow

Physical Mixtures

Powder solid dispersion or physical mixture equivalent to 10 mg of piroxicam was accurately weighed and transferred to a 100 ml volumetric flask. About 30 ml of distilled water was added and flask was shaken to dissolve the contents completely and the volume was made up upto the mark with distilled water. The concentration of this resulting solution was 100µg/ml. From this solution, 1 ml of solution was taken in another 10 ml volumetric flask, and volume was made up upto 10 ml with distilled water. The solution was analysed spectrophotometric at 358.6 nm against corresponding reagent blank. The analysis was carried out in triplicate and drug contents were determined. Results of the analysis were shown in the Table 12.

Table 12.Drug content of piroxicam in solid dispersions and physical mixture

S. No.	Drug: solubilizers ratio	Drug content in % w/w	
		Solid dispersion	Physical mixture
1.	1:4	98.80	99.00
2.	1:6	99.50	100.2
3.	1:8	101.9	99.50
4.	1:10	100.4	101.40
5.	1:12	99.20	100.10

Solubility Study of solid Dispersion[4]

The apparent solubility of solid dispersions of Piroxicam was determined in distilled water. Each solid dispersion in excess quantity was added to 10 ml of solvent in glass vials with rubber closers. Then the vials were kept on a rotary shaker for 12 h. After shaking, the vials were kept in room temperature equilibrium for 24 h. The solution was then filtered through 41 whatman filter paper and the filtrate was assayed spectrophotometric at 358.6 nm. The results were reported in Table 13.

Table 13.Solubility Study of solid dispersion

S.No.	Solid Dispersion	Solubility (mg/ml)
1	SD 1:4	0.386
2	SD1:6	0.512
3	SD 1:8	0.670
4	SD 1:10	0.718
5	SD 1:12	0.732

Fourier Transforms IR Spectroscopy[2]

Fourier-change infrared (FT-IR) spectra were acquired by utilizing Jasco 4100FTIR. The examples of unadulterated piroxicam, actual combination 1:8 and streamlined strong scattering 1:8 was already ground and blended completely with potassium bromide; the FTIR spectra were recorded utilizing KBr scattering technique in the district of 400-4000 cm^{-1}. Spectra were recorded in Figure 1-3.

Powder x-ray diffraction studies (XRD)[12]

X-beam diffraction investigation was performed utilizing Brukeraxs diffractometer D8 Advanced model utilizing Cu radiation which was created at 40 KV and 40mA at 1.540600A. The information was gathered over a rakish reach from 5-609 in constant mode, with test pace of 0.0292. The X-beam diffractogram of the medication test,

actual combination and strong scattering was appeared in Figure 4-6.

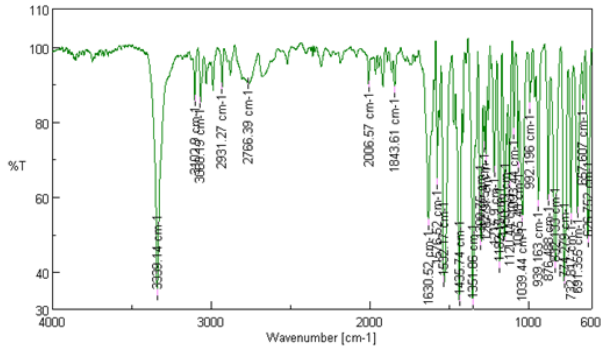


Figure 1.FTIR spectra of piroxicam

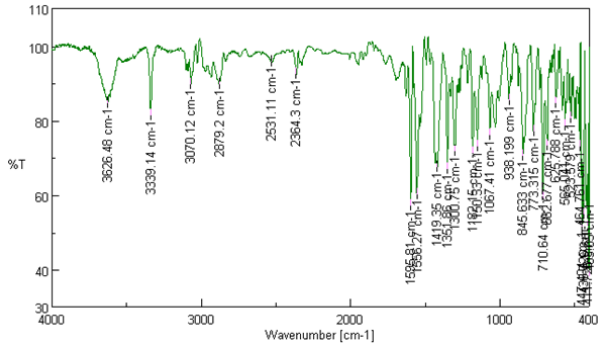


Figure 2.FTIR spectra of physical mixture of 1:8

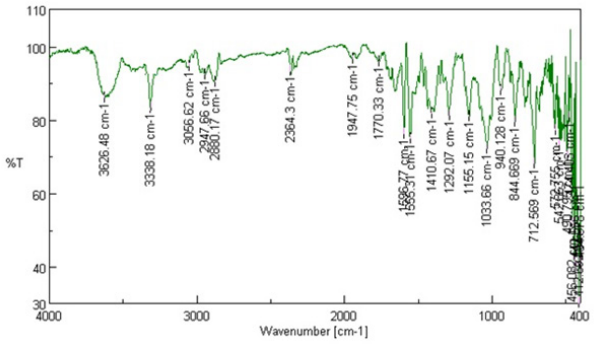


Figure 3.FTIR spectra of Solid dispersion1:8

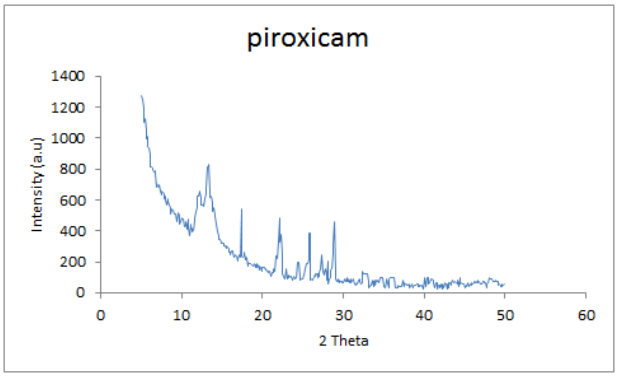


Figure 4.X-ray diffractogram of piroxicam drug sample

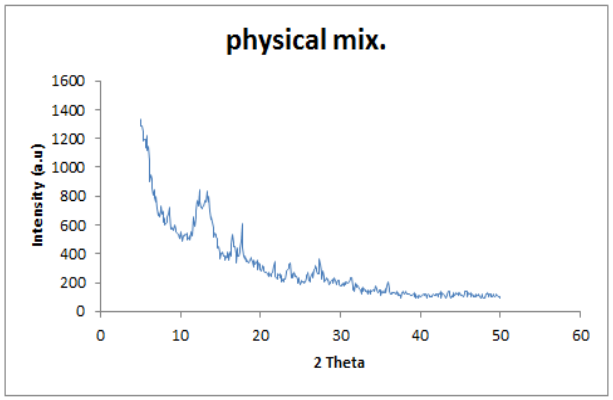


Figure 5.X-ray diffractogramof physical mixture 1:8

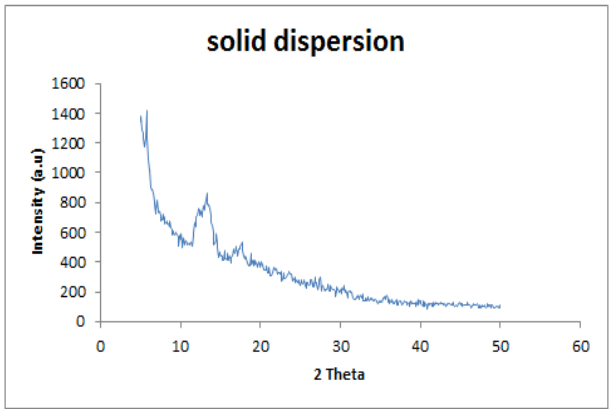


Figure 6.X-ray diffractogram of solid dispersion 1:8

Differential Scanning Calorimetry (DSC)[11]

The DSC study was performed on a Shimadzu (DSC 60) differential filtering calorimeter with warm analyser. Precisely gauged tests (around 3 mg of tests) were set in fixed aluminium dish, prior to warming under nitrogen stream (20 ml/min) at an examining pace of 10*C per min from 20 to 300* C. A vacant aluminium skillet was utilized as reference. The DSC spectrum of pure piroxicam, physical mixture 1:8 and optimised solid dispersion 1:8 is shown in Figure 7-9.

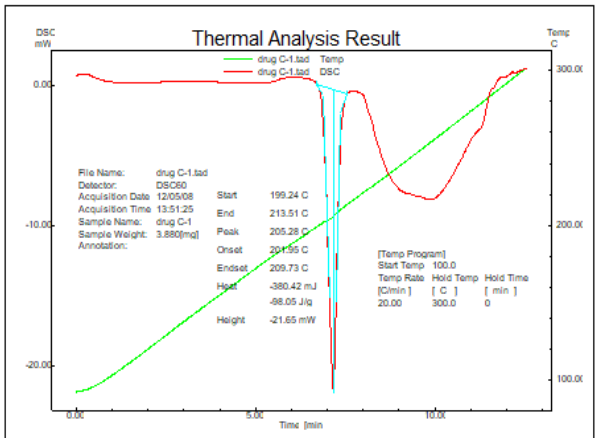


Figure 7.DSC thermogram of piroxicam

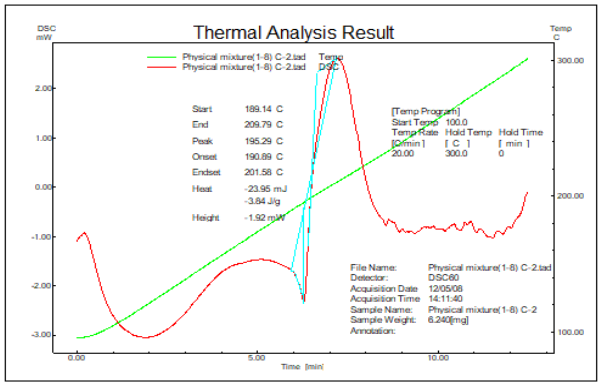


Figure 8.DSC thermogram of physical mixture 1:8

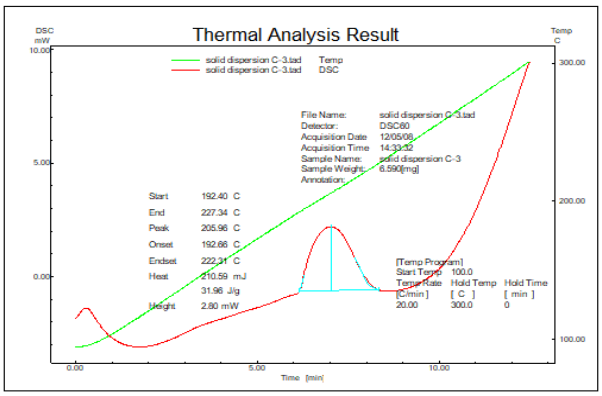


Figure 9.DSC thermogram of physical mixture 1:8

Scanning Electron Microscopy (SEM)[12]

The scanning electron microscopy is a type of electron microscopy that images the sample surface by scanning it with a high-energy beam of electrons. The electrons interact with the atoms that make up the sample producing signals that contain information about the sample's surface photography, composition and other properties such as electrical conductivity.

SEM was utilized to examine strong state actual construction of the readied strong scatterings. S.E.M. photos of piroxicam, its actual blend with hydrotropic specialists and its strong scatterings were gotten utilizing a filtering electron magnifying lens model JEOL JSM 5600 with speeding up voltage from 0.5 to 30 KV. SEM photos were accounted for in Figure 10-13.

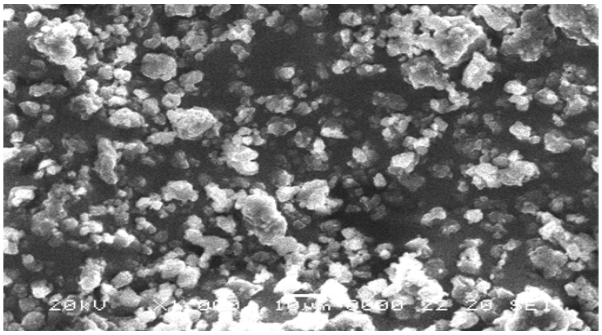


Figure 10.SEM photographs of piroxicam

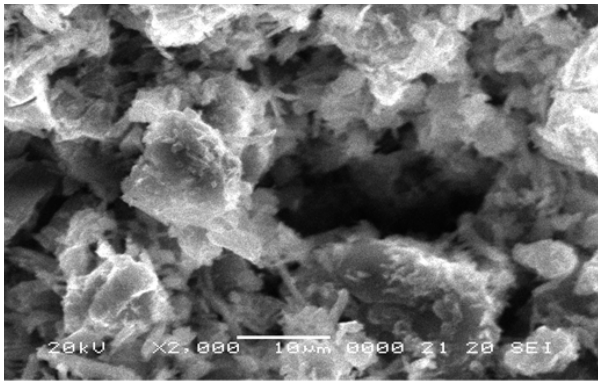


Figure 11.SEM photographs of physical mixture 1:8

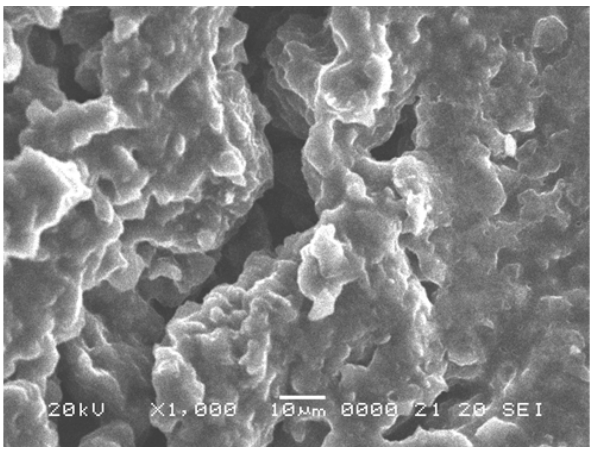


Figure 12.SEM photographs solid dispersion 1:8(10 µm)

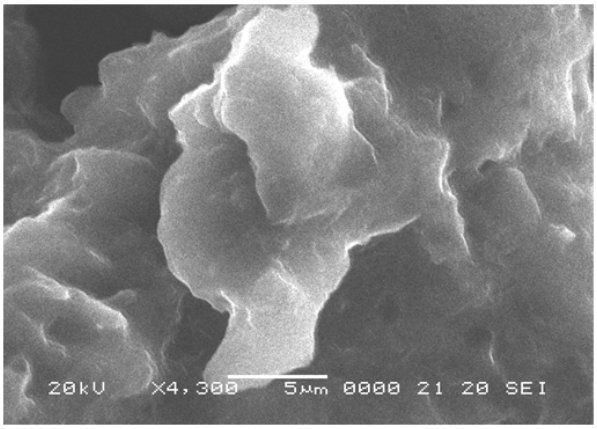


Figure 13.SEM photographs solid dispersion 1:8(5 µm)

Discussions

From the above studies, it is evident that solid dispersions of ratio 1:8 to 1:10 were dissolved nearly completely within 1 minute, and when observed visually, they were found to be dissolved only within 40-50 seconds. While, on the other hand the solid dispersions of ratio 1:4, 1:6 and physical mixture dissolved completely even after 30 minutes.

Since, there was significant improvement in dissolution rate when drug solubilizers were used in 1:8, and 1:10 ratio. The

dissolution profiles from these two solid dispersions were almost same. To minimize the quantity of solubilizing agents, 1:8 ratio was optimum ratio. These capsule formulation withdrawal of sample in 5,10,15,20,25,30 and 35 min. in that shows prepared capsule formulation was better release than that of marketed capsule formulation.

In FTIR study the pure drug piroxicam shows N-H stretching, C=N ring stretching, -SO_2 Asymmetric stretching, N-H bending, C-S Stretching, Ortho disubstituted benzene ring, observed ranges of wavenumber respectively 3339.14, 1532.17, 1300.75, 1576.52, 691.35, 774.27. Peaks given by piroxicam spectra are present in the FTIR spectra of solid dispersions and physical mixture. Only change of percent transmittance due to changes of crystalline to amorphous form.

X-ray diffraction of piroxicam displayed four major peaks shows at diffraction angles (2θ) 13.10°, 13.40°, 18.50°, 22.10°, and 28.90° showing a typical crystalline pattern. However, all major characteristic crystalline peaks appear in the diffractogram of solid dispersions and physical mixture system but of low intensity. This indicates that some amount of drug converts to its amorphous form. IR and DSC studies support same hypothesis, which is confirmed by x-ray diffractometry.

The DSC bend of unadulterated piroxicam showed a solitary endothermic reaction relating to the liquefying of medication. Beginning of dissolving was seen at 201.95°C, where as unadulterated PVP K 30 showed a softening endotherm at 100.41°C. Thermograms of SDs showed the shortfall of a piroxicam top, proposing that piroxicam is totally solvent in the fluid period of polymer or nonattendance of translucent nature of piroxicam. In any case, the dissolving pinnacle of PVP K 30 in SDs was seen at somewhat lower temperature (97-100°C) than that of unadulterated PVP K 30. The PMs Formulation of piroxicam and PVP K 30 likewise showed no endothermic pinnacle of piroxicam. It is hypothesized that piroxicam broke up in PVP K 30 during the DSC estimation, just a single endothermic top at 103.33°C relating to PVP K 30 was noticed.

The strong scattering arranged were additionally portrayed by filtering electron micrographs. SEM of the readied scatterings demonstrates that the granule is unpredictable fit as a fiddle and their size was discovered to be to some degree diminished when contrasted with unadulterated medication. SEM pictures showed that the glasslike piroxicam is changed over to its shapeless structure which is additionally affirmed by DSC and XRD study.

Conclusion

From all the above investigations, it was presumed that the methodology of blended dissolvability is novel, safe, practical and easy to understand. It likewise takes out the issue of harmfulness related with high grouping of water-dissolvable solubilizers. Along these lines, it could be utilized in measurement structure advancement of medications where quick beginning of activity wanted. It might likewise improve the bioavailability related to helpless disintegration of medication.

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