Solubility Enhancement of Hydrophobic Drug Using Solid Dispersion (Kneading Method) of Domperidone

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Abstract:

A saturated solution is a solution in which the dissolved solute is in an equilibrium with solute (solid phase), at an unambiguous temperature. Solubility is one of the critical physicochemical properties of the drug that influences the rate and extent of absorption. It is important for a drug to be in the form of an aqueous solution at the site of absorption for it to be absorbed by the gastrointestinal (GI) tract. In phase solubility studies F1- Pure drug, F2- Drug HPC complex [1:1], F3- Drug β-CD complex [1:1] Discussion: The solubility of domperidone can be enhanced by Formation of complexes F2, F3. In which the formulation F3 increase the solubility by three times as compare to pure drug, The FT-IR of pure drug was characterized by C =O stretching at 1710.60 cm-1, and N-H stretching at 3000 cm–1 .Which indicates the presence of –CONH group, asymmetric C-H stretching at 2937.38 cm-1, symmetric C-H stretching at 2817.81 cm-1, N-H deformation at 1693.38 cm-1. sharp characteristic peaks of domperidone at 600, 700, 1192.40, 1490.12, 1490.12 & 1500 cm-1. All the above characteristic peaks appear in the spectra of dispersion complex F2, and F3.

Keywords: Solubility enhancement, Solubility ratio, inclusion complexes, cyclodextrine, DSC analysis domperidone.

INTRODUCTION

Solubility is defined as the amount of drug solute in a given volume of the solvent system at a certain temperature, pressure and pH. According to IUPAC, solubility is defined as the analytical composition of a saturated solution, consisting of a designated solute in a designated solvent system.[1] A saturated solution is a solution in which the dissolved solute is in an equilibrium with solute (solid phase), at an unambiguous temperature. Solubility is one of the critical physicochemical properties of the drug that influences the rate and extent of absorption. It is important for a drug to be in the form of an aqueous solution at the site of absorption for it to be absorbed by the gastrointestinal (GI) tract.[2] Solubility conduct of the drugs is one of the most challenging characteristics in formulation development. Poorly soluble drugs. A majority of active pharmaceutical ingredients that are being developed (drug) are lipophilic with limited aqueous solubility leading to problems in preclinical pharmacokinetic and toxicological investigations.[3] Due to rapid advancement in combinatorial chemistry, high-throughput screening this increase of poorly aqueous soluble drugs have been observed.[4] Dose: Solubility ratio, a parameter that is used to identify poorly soluble drugs, is defined as the volume of gastrointestinal fluids required to dissolve the administered dose. If this volume exceeds available gastrointestinal fluids, then the drug is likely to have solubility issues.[5] The new drug delivery systems are having an edge over conventional ones in terms of many biopharmaceutical parameters; among such drug delivery systems are controlled/ prolonged release solid dispersion and micro particles/ microsphere.[5] These systems can achieve therapeutically effective concentration of the drug in the systemic circulation over an extended period of time with better patient compliance.[6] Water insoluble carriers are generally used to produce a controlled release formulation.[6] The properties of the carriers have major influences on the release profile of the dispersed drug, specifically the second generation carriers. These carriers include ethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, cellulose acetate phthalate, ethyl acetate, Chitosan, and methacrylic acid copolymers.[7] A variety of approaches can be used to increase the solubilization and bioavailability of poorly water-soluble drugs. Micronization, chemical modification, pH adjustment, solid dispersion, complexation, co-solvency, micellar solubilization, hydrotropy, and other procedures are often used for medication solubilization. Solubilization of poorly soluble pharmaceuticals is a common difficulty in novel chemical entity screening investigations as well as formulation design and development.[8] The ultimate quantity of analyte that may be dissolved in a volume of solvent is known as solubility. It can

be characterised both quantitatively and qualitatively. In qualitative term, it can be defined as Spontaneous interaction of two or more substance to form a homogenous dispersion. In quantitative term, Concentration of a substance (solute) in a given volume of solvent at a certain temperature to form homogenous solution. The solubility of drug maybe expressed as percentage, parts, molality, molarity, mole fraction & volume fraction. In pharmaceuticals, solubility equilibria are very important. Drugs having poor water solubility (BCS class II and class IV) shows dissolution related problems.[9] The BCS is a scientific paradigm for categorizing pharmaceuticals based on their water solubility and intestinal permeability. When paired with the drug product's in vitro dissolving properties, the BCS considers three important factors: solubility, intestinal permeability, and dissolution rate, all of which influence the rate and amount of oral drug absorption from sudden release solid oral-dosage forms. According to the BCS which was classified by US Food & Drug Administration (FDA), pharmaceuticals are classified into four fundamental classes based on their solubility and permeability (Table 1). Drugs of class II & class IV are facing solubility problem. So, increase the solubility turns increase bioavailability of BCS Class II & Class IV drugs.

MATERIAL & METHOD

Domperidone (DOM), was obtained as gift samples from Trade N Trade Tumsar (Glaxo) Cyclodextrine and Hydroxypropyl Cellulose was obtained and all the chemical from the analytical grade supplied from the store room from), the, MIP, Belata India

Domperidone

(DOM), or 5-chloro-1- [1-[3-(2,3-dihydro-2-oxo-1H-benzimidazol-1-yl)propyl]-4-piperidinyl]-1,3- dihydro-2H-benzimidazol-2-one [(C22H24ClN5O2)] is a dopamine antagonist used as an antiemetic for the short-term treatment of nausea and vomiting of various etiologies including that associated with cancer therapy and with levodopa or bromocriptine therapy for parkinsonism.[10] Domperidone is poorly water soluble drug erratically absorbed in stomach and possess several dissolution problems thus it has a poor bioavability [15%]. The poor aqueous solubility may be one possible reason for its low bioavailability.

Cyclodextrine

Cyclodextrinsare mainly used to increases the aqueous solubility and dissolution rate of drug. Among α, β, γ.β-CD are used for the study, because it has bigger cavity size of (7.5A) and is

the least toxic among the other natural cyclodextrin.[11] Cyclodextrins were reported to enhance topical drug delivery in the presence of water. The interior environment of a cyclodextrin cavity is hydrophilic; hence it can entrap unionized form of the molecule which too is hydrophilic, Cyclodextrins (CDs) are polysaccharides made up of six to eight d-glucose monomers connected at the one and four carbon atoms. They having a property of forming inclusion complex with various guest molecules with a suitable polarity and dimension because of their special molecular structure/hydrophobic internal cavity and hydrophilic external surface Owing to this ability, they have found extensive application in many fields including pharmaceutical technology (to improve the aqueous solubility, dissolution rate, bioavailability and stability of drugs).[12] Now, many poorly soluble drugs have been complexed by CDs to enhance solubility, chemical stability and bioavailability of the drugs. When complexed with CDs, many guest molecules exhibit enhanced fluorescence efficiencies, since CD cavity can protect guest molecule excited states from nonradiative and quenching processes that normally readily occur in bulk aqueous solution and the fuorimetric method is sensitive and selective, so it have been extensively used to determine the association constants of complexes . The solid inclusion complex were characterized by methods include infrared spectra (IR), differential scanning calorimetry (DSC), element analysis , the cyclodextrin complex successfully observation include many atoms and have explained the experimental studies.[13]

Hydroxypropyl Cellulose. Cellulose ether derivatives as hydroxypropyl Cellulose are water soluble uncharged polymers they interact with anionic surfactant in the solution resulting in rhelogical properties to the system. It is partially substituted poly (hydroxypropyl) ether of cellulose.[14] It contains not less than 53.4 percent and not more than 80.5 percent of hydroxypropoxy groups. All other material used in the study of analytical grade. In the present work, we prepared the inclusion compound of Domperidone-β-cyclodextrin under microwave irradiation, and determined the complex by FTIR, X-RD studies, DSC, Phase solubility studies etc

Preformulation Studies

Determination of Melting Point

The melting point of Domperidone was determined by capillary tube method. A small quantity of powder was placed into a capillary tube and the tube was placed in the capillary melting apparatus and the temperature was gradually increased automatically.[16] The

temperature at which powder started to melt and the temperature when all the powder gets melted were observed.[15]

Solubility studies

Drug solubility is usually determined by the equilibrium solubility method in which excess amounts of drug were taken and 10 ml of the respective distilled water and 0.1 N HCl transferred in to 100 ml stopper volumetric flask and shaken for 24 hour at room temperature [25ºC] samples were filtered through watt Mann filter paper no.42 and aliquots were suitably diluted for estimation and measure the absorbance at 284 nm. (Shimadzu UV- 1800, Japan)

Calibration curve of Domperidone

A stock solution of Domperidone [10 mg] was prepared and transferred to 100 ml calibrated volumetric flask then 1 ml Dimethyl sulfoxide [DMSO] was added and make up the volume with 0.1N HCl. From this stock solution, 10 ml was pipette out and diluted to 100 ml with 0.1 N HCL. Further dilutions were made in order to obtain the solutions of 2, 4, 6, 8 and 10µg/ml respectively. Measured the absorbance in UV Spectrophotometer at µnmax284 nm against reference solvent as a blank. The drug in the concentration range of 2–10 mg/ml was found to obey Beer–Lambert‟s law. Repeat the same procedure using distilled water as solvent. The calibration curve was plotted taking concentration on X-axis and absorbance on Y-axis

Preparation of inclusion complexes

Domperidone inclusion complexes were prepared by using β- CD and HPC [1:1] with a mixture of volatile liquid (acetone) and water (1:1) and kneaded thoroughly for 30 minutes in a motor and pestle. Sufficient solvent was added to maintain paste like consistency. The paste formed obtains and dried under vacuum for 24 hours. Dried powder were scrapped, crushed, pulverized and passed through sieve no. 80 and stored in desiccators for further studies.

Phase solubility studies

Phase solubility studies were performed according to the method suggest by Higuchi and Connors. An excess amount of Domperidone (10 mg) was added to 10 ml of distilled water containing rising amounts of β-CD and HPC solutions at various concentrations (0, 2, 4, 6, 8, 10 µg/ml) in 50 ml volumetric flask . The solution were stirred at 37°C for 24 hours on a Orbital Shaking Incubator REMI Elektrotechnik Limited, (Model no. CIS-24BL). After equilibrium, the samples were filtered through Wattmann filter paper no. 42 and measure the

absorbance at λmax 284 nm using a UV spectrophotometer (Shimadzu UV- 1800 Spectrophotometer, Shimadzu, Japan). The apparent 1:1 stability constant of the complex was calculated from the phase-solubility diagram using the following equation. Apparent stability constant

Where S- slope, So- intercept

Fourier Transform Infra-Red Spectroscopy

The FT-IR spectra of pure drug, Drug and physical mixtures were taken by preparing KBr pellets using FTIR spectrophotometer (Varian640-IR, USA). The condition was used as follows pressure, 6-8 tons; die size, 13mm; The spectra were recorded within 4000-400cm-1 wave numbers.

Differential scanning calorimetry (DSC) is a thermoanalytical technique in which the difference in the amount of heat required to increase the temperature of a sample and reference is measured as a function of temperature. Both the sample and reference are maintained at nearly the same temperature throughout the experiment. Generally, the temperature program for a DSC analysis is designed such that the sample holder temperature increases linearly as a function of time. The reference sample should have a well-defined heat capacity over the range of temperatures to be scanned. Additionally, the reference sample must be stable, of high purity, and must not experience much change across the temperature scan. Typically, reference standards have been metals such as indium, tin, bismuth, and lead, but other standards such as polyethylene and fatty acids have been proposed to study polymers and organic compounds, respectively.

RESULT & DISCUSSION

Determination of Melting Point

Domperidone is a white, crystalline odourless powder. The physical appearance was found to be similar with that of the reported standards of European Pharmacopoeia. Melting point the drugs was determined by using melting Point determination apparatus 242-244oC. This compiles the specifications of the pure drug as per European Pharmacopoeia.

Solubility studies

The solubility of Domperidone in Distil water is 3.68 µg/ml and in 0.1 N Hcl is 13.82 µg/ml. Formation of complexes between Drug, β-Cyclodextrins, and Hydroxypropyl cellulose increases the solubility compare to pure drug in both the distil water and 0.1 N HCL.

Standard curve

Discussion: As per the observations Standard curve for domperidone in 0.1 N Hcl and distal water at λmax max 284 with varying concentration range of 2, 4, 6, 8, 10 µg/ It was found that the estimation of domperidone by spectrophotmetric method at 284nm. The calibration curve equation for domperidone in 0.1 N HCL was obtain $Y = 0.028\ X + 0.000$, with correlation coefficient $r2 = 0.998$, and in Distil water were obtain = $0.016\ X + 0.001$ with correlation coefficient $r2 = 0.998$ respectively. This proves the linearity, of the curve.

Fourier Transform Infrared Spectroscopy FTIR

FTIR spectroscopy was used to characterize the possible interactions between drug and carrier in the solid state. The FT-IR of pure drug was characterized by C =O stretching at 1710.60 cm-1, and N-H stretching at 3000 cm–1 .Which indicates the presence of –CONH group, asymmetric C-H stretching at 2937.38 cm-1, symmetric C-H stretching at 2817.81 cm-1, N-H deformation at 1693.38 cm-1. sharp characteristic peaks of domperidone at 600, 700, 1192.40, 1490.12, 1490.12 & 1500 cm-1. All the above characteristic peaks appear in the spectra of dispersion complex F2, and F3. Systems at same wave number which indicate no modification or interaction between the drug and polymers. Shown in figure

Phase solubility studies

The phase solubility diagram for the complex formation between F2 and F3 is shown in figure 6. For F2 the regressed curve has a slope value 0.011, intercept 7.8x 10 -2mM and correlation coefficient is r = 0.968 and F3 the regressed curve has a slope value 0.015, intercept 7.5x10-2 mM and correlation coefficient is r = 0.989, and the phase solubility diagram figure 2 showed AL type of curve, due to the straight line had a slope less than unity; indicates the formation of complex. The apparent stability constant, K was calculated from the linear plot of the phase solubility diagram according to the equation.

Apparent stability constant K= SLOPE/ so (1-SLOPE)

Where, „S0‟ is the slope, and so is the intercept. The apparent stability constant, „K‟ of F2 and F3 was found to be 142 M-1, 200.3 M-1 respectively. This indicates the formation solid complexes prepared by kneading method.

Table no.4. Solubility analysis of pure drug and different ratio of polymers

Samples	Solubility Distilledwater (µg/ml)	Solubility 0.1 N Hcl (µg/ml)
F1	3.68	13.82
F2	8.416	21.85
F3	10.66.	30.81

F4	7.06	15.86
F5	8.76	17.65
F6	9.43	17.90

F1- Pure drug, F2- Drug HPC complex [1:1], F3- Drug β-CD complex [1:1]

Discussion: The solubility of domperidone can be enhanced by Formation of complexes F2, F3. In which the formulation **F3 increase the solubility by three times as compare to pure drug**

Table no.5. Preparation of STD Curve of Domperidone in 0.1 N HCL

Con	Abs -1	Abs -2	Abs -3	Average	Std dev
0	0	0	0	0	0
2	0.063	0.06	0.047	0.057	0.009
4	0.143	0.114	0.099	0.119	0.022
6	0.188	0.167	0.142	0.166	0.023
8	0.244	0.227	0.221	0.231	0.012
10	0.288	0.311	0.267	0.289	0.022

Table no.6. Preparation of STD curve of Domperidone in Distilled water

Con	Abs -1	Abs- 2	Abs-3	Average	Std.Dev
0	0	0	0	0	0
1	0.017	0.012	0.014	0.014	0.003
2	0.032	0.033	0.031	0.032	0.001
4	0.058	0.063	0.068	0.063	0.005
6	0.082	0.098	0.101	0.094	0.010
8	0.106	0.114	0.14	0.120	0.018
10	0.132	0.142	0.167	0.147	0.018

Figure no.5. Drug + β-Cyclodextrins complex 1:1

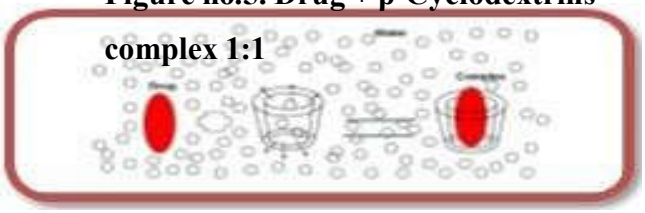
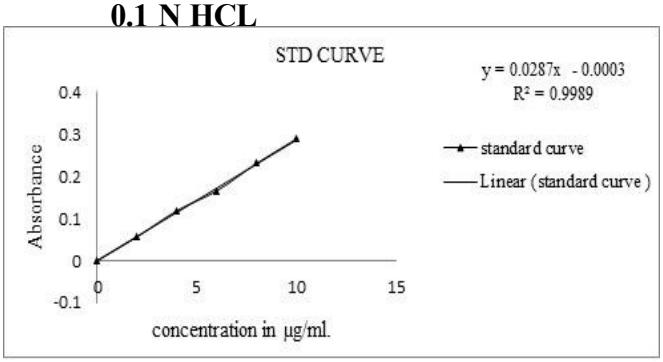


Figure no.6. Complexes 1:1.

Figure no.7. sample for phase solubility studies

Figure no.8. orbital shaker assembly

Domperidone in 0.1 N HCL



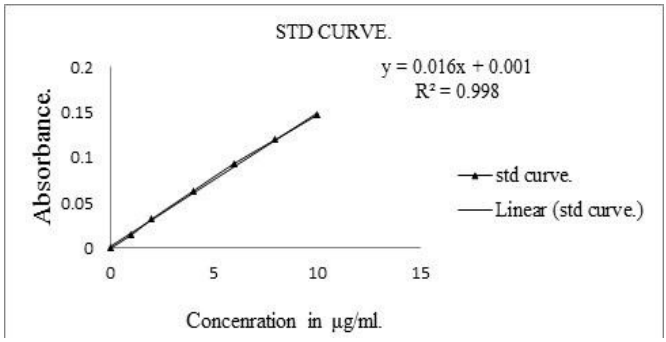


Figure no.9. Preparation of STD Curve of Domperidone in Distilled water

Figure no.10 Preparation of STD curve of

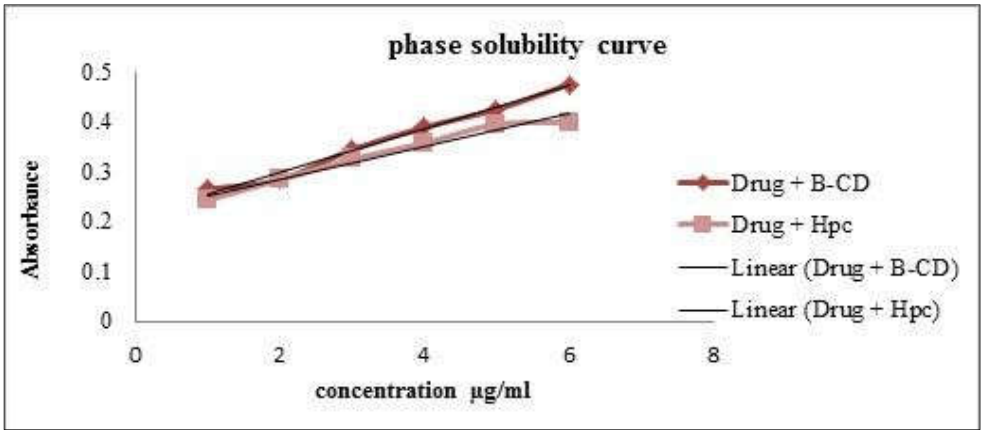


Figure 11. The phase solubility diagram Domperidone and β-Cyclodextrins and Hydroxypropyl cellulose at 28°c

Figure 12.1: F-1[Pure drug]

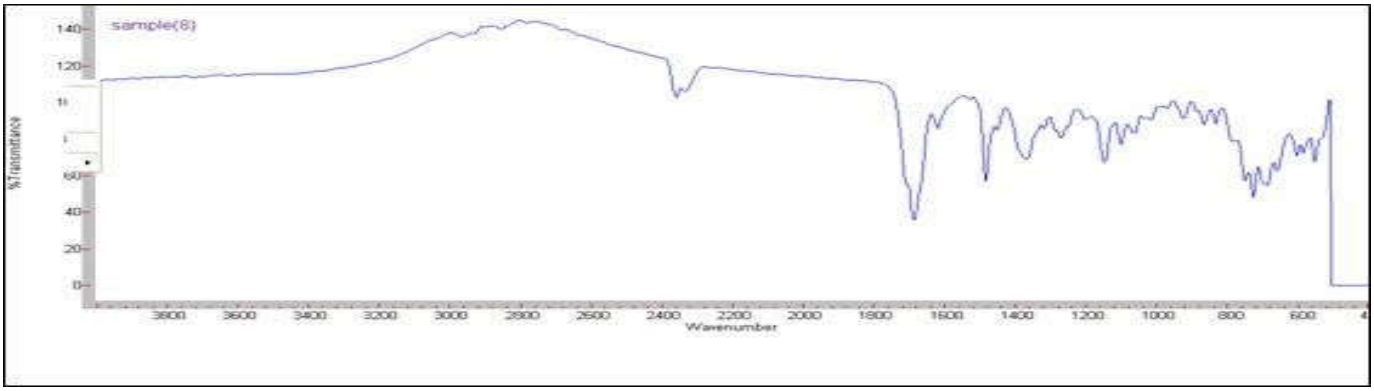


Figure 12.2: F-2 [Drug + HPC].

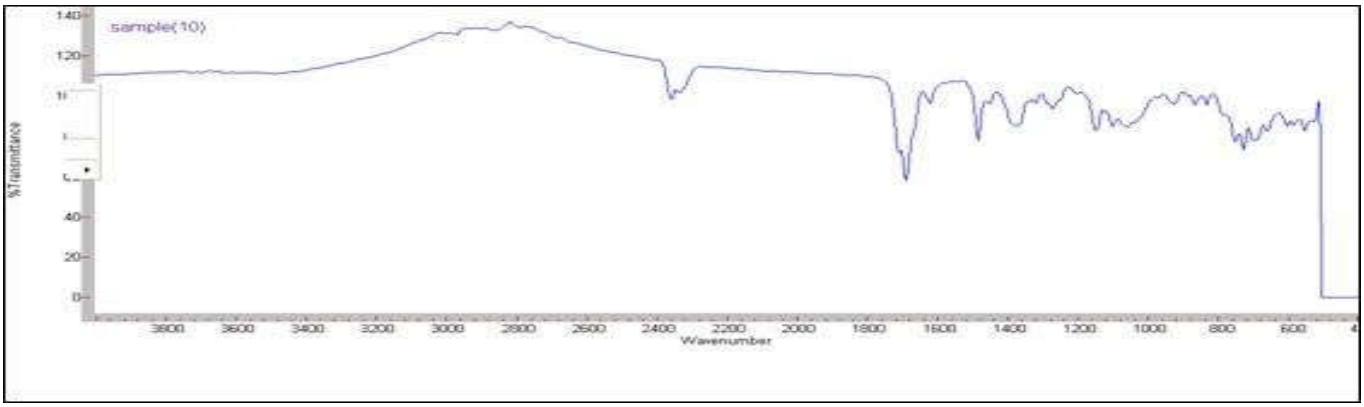
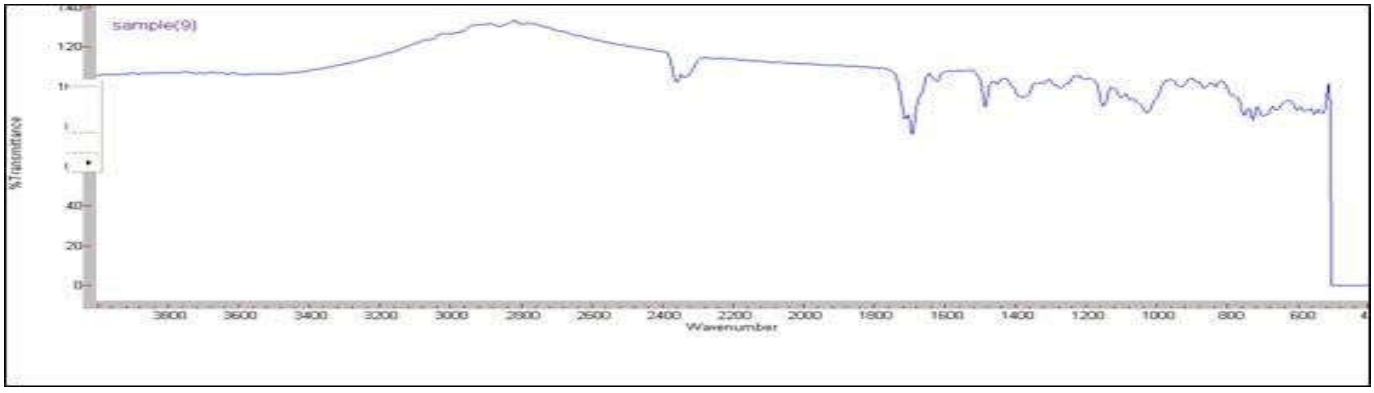


Figure 12.3: F-3 [Drug + β-CD].



DSC (Differential scanning calorimetry)

The DSC studies were conducted using a Thermal Analysis DSCQ100 differential scanning calorimeter (Madhyachl university Bhopal). DSC thermogram of domperidone as in figure 13) showed a sharp endothermic peak at 249ºC, this melting point of pure domperidone that the drug has crystalline nature with high purity. DSC of PVP-K15 as in figure (13.1) showed broad peak of water evaporation at 107º C this indicate amorphous nature of this polymer. Physical mixture of PVP-K15:pure domperidone (2:1) showed broad and low intensity peak of domperidone which is nearly at same position within the range of melting point in figure (13.2). This indicates no chemical reaction or complexation between drug and polymer, DSC figure (13.3) showed remarkable reduction in peak intensity in comparison with pure domperidone, that indicates a reduction of crystalline state of domperidone and conversion of part of it to amorphous state, this result with that obtained X-ray diffraction analysis.

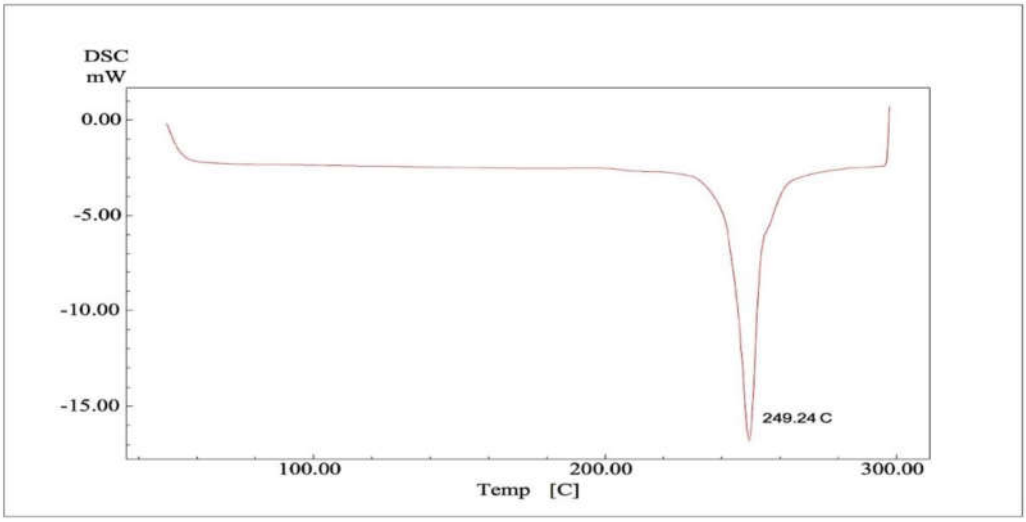


Figure no.13. DSC thermogram of pure domperidone

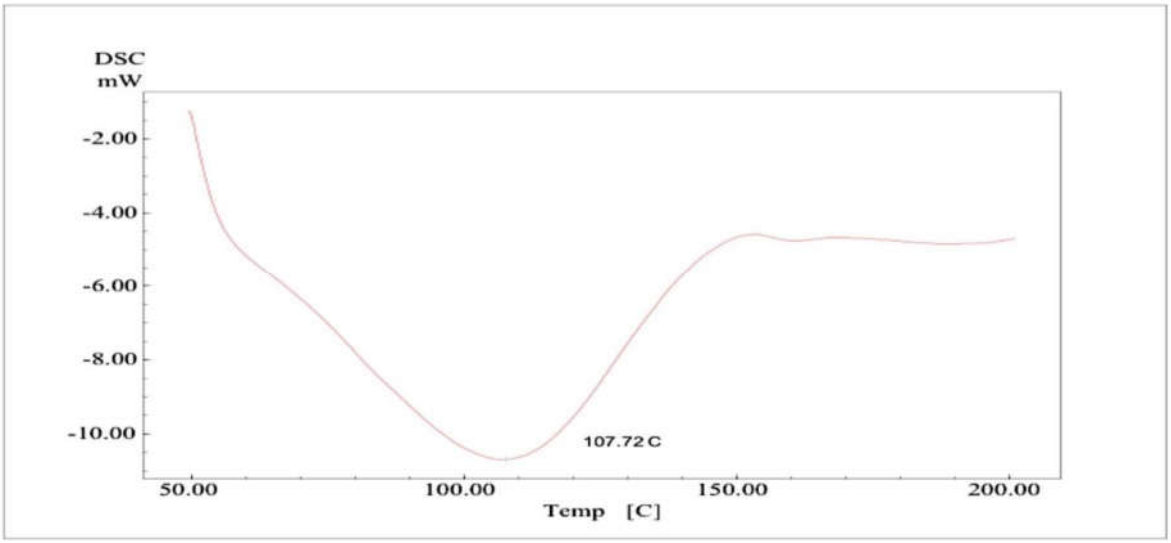


Figure no.13.1. DSC thermogram of PVP-K15

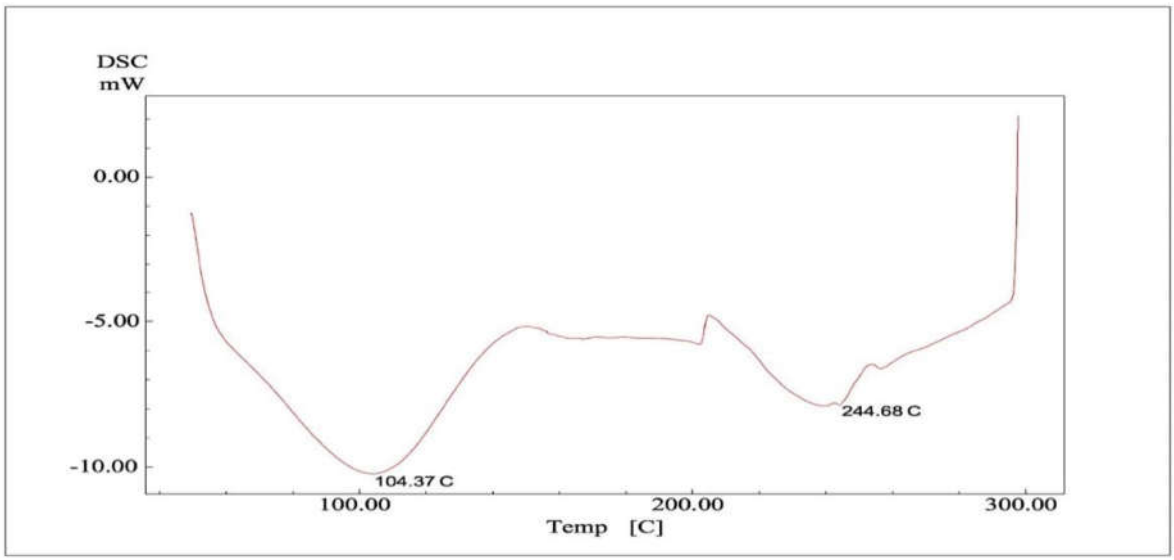


Figure no.13.2. DSC thermogram of physical mixture of PVP-K15:pure domperidone (2:1)

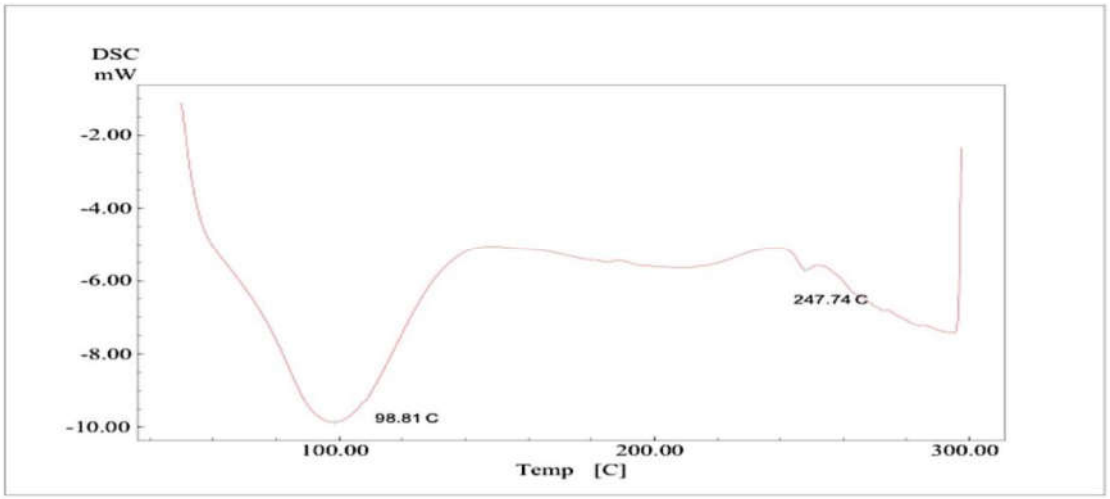


Figure no.13.3. DSC thermogram of domperidone

Drug Release Pattern of solid dispersion

In Vitro Drug release study

The release studies were carried out in 900 ml beaker containing 100 ml Phosphate buffer. Phosphate buffer pH 7.4 (100 ml) was placed in a 900 ml beaker. The beaker was assembled on a magnetic stirrer and the medium was equilibrated at 37±50C.

Time (min)	**Batch code**					
0	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
5	17.38	19. 17	43.09	19. 17	22.80	36.14

10	24.07	23.63	52.12	23.63	25.18	45.52
20	27.14	26.10	60.26	26.10	28.32	53.21
30	30.32	30.35	69.10	30.35	31.72	62.20
45	31.85	32.62	87.39	32.62	32.35	72.65
6o	34.41	34.44	92.88	34.44	36.54	81.48

(Mean ± S.D., n=3) Figure 14: in vitro drug release of various formulations

All the three batches of formulation F3 were found to release the drug in 1 h. The cumulative percentage release was found to be 92.88%.

Study of drug release kinetics

Drug release kinetics for formulations F3 were shown in table & figure which follows the Higuchi's and Peppas Korsmeyer's plot respectively.

Crystallinity studies

All SDs were prepared via solvent evaporation method in a rotary evaporator. The SD components (drug, and polymer) were dissolved 90:10 v/v DCM:MeOH. Once dissolved, the solvent removal was performed using a Buchi Rotavapor-R210 (New Castle, DE) at 45°C under vacuum. Once dried, the SDs were further dried overnight in a vacuum oven to a volatile content of less than 1.4% (determined by TGA). The SD samples were examined by PLM and PXRD to ensure no detectable crystals were present (data not shown). The resultant SDs were milled and the fraction of 45-250 mm particles was collected. API crystals were then spiked into these SDs to create crystallinity at 0% (control), 5% and 10% w/w. The composition of all formulations is described in. For the slow crystallizer ABT-450, six SD samples were made covering two drug loadings (DL of 10% and 40%), and each DL was spiked at crystallinity of 0%, 5% and 10%. For the fast crystallizer, felodipine, 12 SD samples were prepared by varying polymer type (copovidone and HPMCAS), DL (10% and 50%) and crystallinity% (0%, 5% and 10%). Vitamin E TPGS was added at 7% w/w across all formulations due to the fact that this surfactant is one of the most frequently used surfactants in amorphous solid dispersions. The use of HPMCAS in Domperidone SDs draws on the previous knowledge that HPMCAS is

a better crystallization inhibitor than copovidone for the fast crystallizer felodipine. Before dissolution testing, the powdered SD samples were filled into clear gelatin capsules.[16] For ABT-450, the capsules were filled at 75 mg dose per capsule, the same dose strength as in the commercial product of Viekira Pak. For felodipine, 8 mg dose was selected. A dose higher than 8 mg will not be soluble in 900 mL buffer. The human doses of Domperidone drug product Plendil (made with crystalline DOM Complex) are 2.5 mg, 5 mg and 10 mg.26 Thus, the selected 8 mg is within the relevant dose range[17]. The drug weight in SD sample remained consistent in all samples, for example, if 5% crystalline API was added, the amount of amorphous API was reduced by the same 5%.

CONCLUSION

The present research work is to enhance the solubility of poorly soluble drug domperidone and conversion in to granules using β-Cyclodextrins and HPC. Domperidone is a drug belongs to a *class II* of drugs called *antiemetic* used for the management of mild to moderate pain, fever, and inflammation. Domperidone having the poor solubility in water about 0.000986 mg/ml and this limits its use as solid dosage form for oral administration, erratically absorbed in stomach and possesses several dissolution-related problems thus it has poor bioavailability. Hence, by considering these facts related to drug, attempts have been made to formulate inclusion complexes using β-Cyclodextrins and also to study the effect of preparation method. Inclusion complexes were prepared using β-Cyclodextrins in 1:1 molar ratios. The solubility of domperidone can be enhance by formation of complexes between Drug, β-Cyclodextrins, and Hydroxypropyl cellulose increase by three times as compare to pure drug as the solubility enhances dissolution rates can be increases and hence increases in bioavability. After performing compatibilities studies FTIR all the characteristic peaks appear in the spectra of dispersion complex F2, and F3. Systems at same wave number which indicate no modification or interaction between the drug and polymers. In Phase solubility studies it was concluded that as the concentration of polymer concentration β-CD and hydroxypropyl cellulose concentration increases, it increases the solubility of Domperidone. The phase solubility diagram Figure 7 showed AL type of curve, due to the straight line had a slope less than unity, indicates the formation of complex. The Apparent stability constant, „K" for F 2 and F3 was found to be *142* M^{-1}, *200.3* M^{-1} respectively. This indicates the formation of stable complex.

REFERENCE

1. Jagtap YM, Bhujbal RK, Ranade AN, et al. Effect of various polymers concentrations on physicochemical properties of floating microspheres. Indian J Pharm Sci 2012;74(6):512–520.
2. Jain SK, Awasthi AM, Jain NK, et al. Calcium silicate based microspheres of repaglinide for gastroretentive floating drug delivery: preparation and in vitro characterization. J Control Release 2005;107:300–309.
3. Jang DJ, Jeong EJ, Lee HM, Kim BC, Lim SJ, Kim CK. Improvement of bioavailability and photostability of amlodipine using redispersible dry emulsion. Eur J Pharm Sci, 28, 2006, 405–411.
4. Jansook, Phatsawee, Ogawa, Noriko, Loftsson, Thorsteinn, 2018. Cyclodextrins: structure, physicochemical properties and pharmaceutical applications. Int. J. Pharm. 535 (1-2), 272–284.
5. Jones, D.S., Dressman, J.B., Loftsson, T., Moya-Ortega, M.D., Alvarez-Lorenzo, C., Concheiro, A., 2016. Pharmacokinetics of cyclodextrins and drugs after oral and parenteral administration of drug/cyclodextrin complexes. J. Pharm. Pharmacol. 68, 544–555.
6. Kaiyawet, Nopporn, Rungrotmongkol, Thanyada, Hannongbua, Supot, 2013. Effect of halogen substitutions on dUMP to stability of thymidylate synthase/dUMP/mTHF ternary complex using molecular dynamics simulation. J. Chem. Inf. Model. 53 (6), 1315–1323.
7. Kalhapure RS, Palekar S, Patel K, Monpara J. Nanocrystals for controlled delivery: state of the art and approved drug products. Expert Opin Drug Deliv 2022;19:1303e16.
8. Kang BK, Lee JS, Chon SK, Jeong SY, Yuk SH, Khang G, Lee HB, Cho SH. Development of self-microemulsifying drug delivery systems (SMEDDS) for oral bioavailability enhancement of simvastatin in beagle dogs. Int J Pharm 274 (1-2), 2004, 65–73.
9. Kirschner, Karl N., Yongye, Austin B., Tschampel, Sarah M., Gonz´alez-Outeiri˜no, Jorge, Daniels, Charlisa R., Foley, B. Lachele, Woods, Robert J., 2008. GLYCAM06: A generalizable biomolecular force field. carbohydrates. J. Comput. Chem. 29 (4), 622–655.

10. Rakesh Tiwle “An Exhaustive Review On Solubility Enhancement For Hydrophobic Compounds By Possible Applications Of Novel Techniques.” Science Alert – Trends Research In Applied Science And Research. 7(8): 596-619; 2012.

11. L.W. Jia, H., Wang, Y., Garza, M., Weitman, S.D. Carbendazim: dispostion, cellular permeability, metabolite identification, and pharmacokinetic comparison with its nanoparticle. Journal of Pharmaceutical Science. 92:161-172 (2003).
12. Liu, Peng, et al. "Nanosuspensions of poorly soluble drugs: preparation and development by wet milling." International journal of pharmaceutics 411.1 (2011): 215-222.
13. Lloyd GR, Craig DQ, Smith A. A calorimetric investigation into the interaction between paracetamol and polyethylene glycol 4000 in physical mixes and solid dispersions. Eur J Pharm Biopharm 1999;48:59–65.
14. Masters, Keith. "Spray drying handbook." Spray drying handbook. (1985).
15. Meng J, Zheng L. Application of mixture experimental design to simvastatin apparent solubility predictions in the microemulsifion formed by self-microemulsifying. Drug Dev Ind Pharm 33 (9), 2007, 927–31.
16. Rakesh Dayaram Tiwle, Research Scholar (Pharmacy), Enhancing Dissolution Rates in Fast-Dissolving Tablets of Antiemetic Agents: Formulation Strategies, International Advance Journal of Engineering, Science and Management (IAJESM) July-December 2023, Submitted in November 2023
17. Loftsson T, Brewster ME. Pharmaceutical applications of cyclodextrins:basic science and product development. J Pharm Pharmacol 2010;62:1607e21.