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Research Article

Formulation and evaluation of bioadhesive buccal Films of Domperidone co-crystals by using Tamarind kernel powder as mucoadhesive polymer

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Abstract

As solubility plays key role in drug dissolution and bioavailability lots of techniques to enhance solubility are evolved. One of the techniques is co crystallization. The main aim of the work is to enhance the solubility of domperidone by co crystallization using coformers like Para amino benzoic acid and succinic acid. The cocrystals were evaluated for melting point and solubility enhancement. these cocrystals were used to prepare buccal films by solvent casting method. In the preparation of buccal films Tamarind kernel powder obtained from the seeds of Tamarind is used as mucoadhesive polymer and Hydroxy propyl methyl cellulose as film former, Polyethylene glycol 6000 as plasticizer, dehydrated banana powder as super disintegrant, sodium saccharin as sweetener and mixture of ethanol and water as solvents. The mucoadhesive strength of Tamarind kernel powder was determined using modified physical balance method. Four buccal films were prepared in which PDBF1 and PDBF2 are the two buccal films prepared using cocrystals of domperidone and Para amino benzoic acid and other two buccal films SDBF1 and SDBF2 with cocrystals of domperidone and Succinic acid. The buccal films were evaluated for different tests like folding endurance, swelling index and Surface pH. In vitro diffusion studies were conducted by Franz diffusion cell using egg membrane as semipermeable membrane and phosphate buffer of pH 7.4. The buccal films prepared with cocrystals of domperidone and succinic acid at weight ratio 1:2 has shown 86%drug release. The work has concluded that there is fold increase in aqueous solubility of Domperidone and the optimized formula is SDBF2 and Tamarind kernel powder can be used as mucoadhesive polymer in novel drug delivery systems.

Keywords: co crystals, solvent evaporation, muco adhesive, buccal films, solvent evaporation

INTRODUCTION:

A multi-component crystalline system is not new but recently the term co-crystal has gained momentum in the glossary of the pharmaceutical world. The physicochemical properties of a drug like melting point, hygroscopicity, solubility, dissolution, and stability are improved for better drug bioavailability, which leads to gain better therapeutic effect of the drug with reduced adverse effects. Solubility as well as dissolution is some of the mechanical characteristics of an active pharmaceutical ingredient (API) that should be thoroughly studied in pharmaceutical drug development.[1]

The buccal delivery of drugs has recently emerged as an effective and safe alternative over other conventional routes of drug administration. Buccal administration easily releases the loaded drug into the buccal cavity for either local or systemic effects. This route of administration is especially suitable in pediatric and geriatric, where patients often struggle to ingest traditional oral solid dosage forms. Moreover, the buccal route is very convenient for drugs that are inactivated in the gastric environment, drugs that irritate the gastrointestinal tract, and during nausea and vomiting episodes.[2]

Bio adhesive mucosal dosage forms including adhesive tablets, gels and patches are outcomes of technological development. Among various dosage forms, the use of polymeric films for delivering medication into buccal cavity has developed great potential in recent era.[3].

Domperidone is prescribed for prevention of chemotherapy-induced nausea and for pre-and post-surgical nausea and vomiting. It is an antiemetic drug that blocks the action of dopamine and has strong affinities for the D2 and D3 dopamine receptors. It is well absorbed from GIT, but its bioavailability is low due to extensive first pass metabolism. This condition makes it a suitable drug candidate for Mouth Dissolving Films[4].

In order to provide a convenient and effective mean of administration of drug to patients suffering from vomiting and nausea, the present study was aimed at developing a rapid onset, fast acting, "patient friendly" and stable mouth dissolving film of Domperidone cocrystals using HPMC and tamarind kernel powder.

MATERIALS

Tamarind seeds were obtained from local market, tagarapuvalasa, Visakhapatnam, Andharapradesh. Domperidone, other polymers and solvents were purchased from yarrow chemicals, Mumbai, India.

METHODS

Flow chart of work

Step1: Extraction of tamarind kernel powder from the seeds

Step2: Evaluation of tamarind kernel powder

Step3: Standard graph construction of domperidone in various buffers

Step4: Preparation of cocrystals of domperidone

Step 5: Evaluation of cocrystals

Step6: Preparation of buccal films of domperidone cocrystals

Step7: Evaluation of buccal films and optimization

Extraction of tamarind kernel powder: Tamarind seeds were collected and dried in sunlight. The kernels are than crushed to fine powder. 20g of fine kernel powder was added to 200ml of cold distilled water to prepare slurry. The slurry obtained is than poured into 800ml of boiling distilled water and are boiled for 20min on a water-bath; a clear solution was centrifuged at 5000 rpm for 20min to separate all foreign matter. Supernatant liquid was separated.[5]

Evaluation of tamarind kernel powder:

Flow properties of the extracted tamarind kernel powder was measured and the values were given in the table2.the mucoadhesive strength of tamarind kernel powder was determined by modified physical balance method and results were given in table 3.

A modified balance method used for determining the ex vivo mucoadhesive strength. Fresh goat mucosa was obtained and used within 2hr of slaughter. The mucosal membrane separated by removing underlying fat and loose tissues. The membrane was washed with distilled water and then with pH6.8 phosphate buffer at 37^0C. The mucosa was cut into the pieces and washed. A piece of mucosa was tied to the Teflon piece, which was kept in beaker filled with pH6.8 phosphate buffer, at 37^0C. The Teflon pieceswas tightly fitted into a glass beaker so that it just touched the mucosa surface. The bioadhesive patch was stuck to the lower side of a pan. The weight was kept in the right-hand pan, which lowered the pan along with patch over the mucosa. The balance was kept in this position for 5min to provide contact time for bioadhesion. The weight was removed and measured.[6]

Force of adhesion (N)= [bioadhesive strength]*9.81]/1000

Bond strength($N\text{-}m^{-2}$)= Force of adhesion/Disc surface area

Preparation of Co-Crystals: solvent evaporation method

The accurately weighed concentration of drug and co-former were dissolved in sufficient amount of solvent on heating until complete dissolution of drug and left for slow evaporation for 24hrs and observed for formation of co-crystals. Trails were made with different co-formers like succinic acid, Para amino benzoic acid, tartaric acid, citric acid, and by using solvent as ethanol.From the trials it was found that co-crystals of domperidone were formed using succinic acid and Para amino benzoic acid (1:1, 1:2) as a co-former. Hence further studies were continued by synthesizing co-crystals of domperidone with succinic acid and Para amino benzoic acid in the ratios 1:1, 1:2.[7]

Construction of Standard graph of Domperidone in various solvents:

For the construction of standard graph 50mg drug was dissolved in 50ml solvent. From this stock solution various concentrations were prepared by suitable dilution with the corresponding solvent and the absorbance was measured against suitable solvents as blank at lambda max and the values were given in table

Solubility enhancement ratio:

The cocrystals of domperidone equivalent to 10mg drug was weighed and dissolved in 100ml water. Suitable dilutions were made and absorbance was measured in uv spectrophotometer at lambda max and the vresults were given in table no5.

Preparation of Domperidone buccal films:

Mucoadhesive buccal film of domperidone was prepared by solvent casting technique using a film forming mucoadhesive polymer. The polymers HPMC K15, PEG 6000 were weighed accurately and dissolved in 5ml ethanol. In another beaker Tamarind kernel powder, Dehydrated banana powder, drug and co-former and sodium saccharin were dissolved in a sufficient quantity of solvent. Then the drug containing solution and polymeric solution are mixed evenly to form a homogeneous casting solution. The whole solution poured in the pre-lubricated glass petri-plate at 40C and left for 12 hr. The film was removed carefully after drying and cut into 2*2 cm. The film was stored in butter paper covered with aluminium foil and stored at room temperature. Similarly 4 patches are prepared with succinic acid and paba with 1:1 and 1:2 ratio.[8]

Table 1: Formulation of domperidone buccal films:

Excepient	PDBF1	PDBF2	SDBF1	SDBF2
Drug and co former	Equivalent to 150mg drug	Equivalent to 150mg drug	Equivalent to 150mg drug	Equivalent to 150mg drug
HPMC K15	500mg	400mg	500mg	400mg
PEG 6000	200mg	200mg	200mg	200mg
Tamarind kernel powder	50mg	50mg	50mg	50mg
Dehydrated banana powder	20mg	20mg	20mg	20mg
Sodium Saccharin	20mg	20mg	20mg	20mg
Ethanol , Water	10ml q.s	10ml q.s	10ml q.s	10ml q.s

RESULTS AND DISCUSSION:

Table 2: Flow properties of Tamarind kernel powder

Bulk density	0.59
Porosity	1.29
Compressibility index	5.78
Angle of repose	27.9
Hausners ratio	1.45
Porosity	1.46

The flow properties of tamarind kernel powder indicates that the powder is free flowing and pluffy.

Figure1: FTIR of Pure Domperiodne

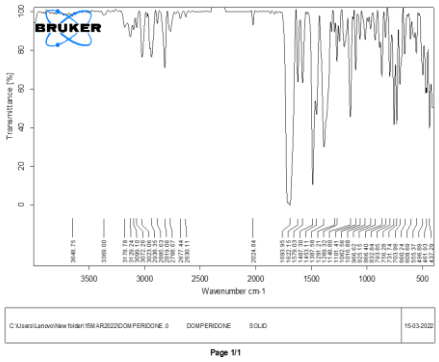


Figure 2: FTIR of Pure Para amino benzoic acid

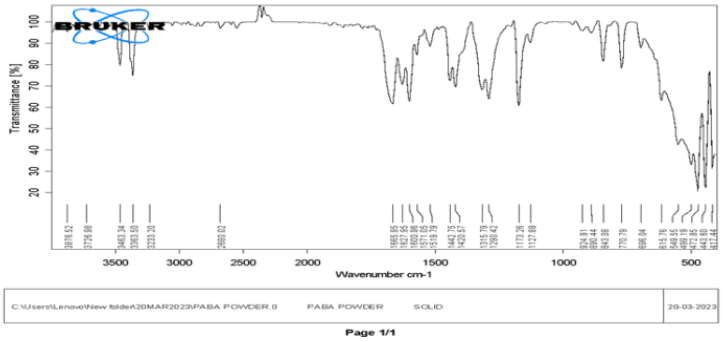


Figure 4: FTIR of pure succinic acid

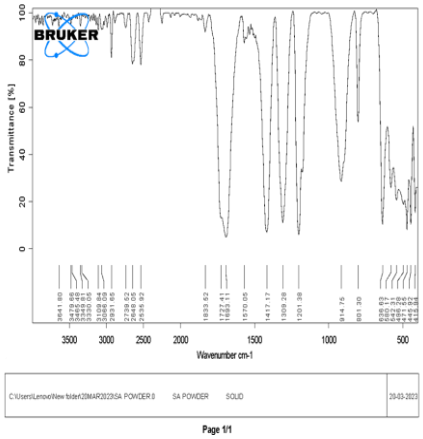


Figure 5: FTIR of cocrystals of drug and Para amino benzoic acid

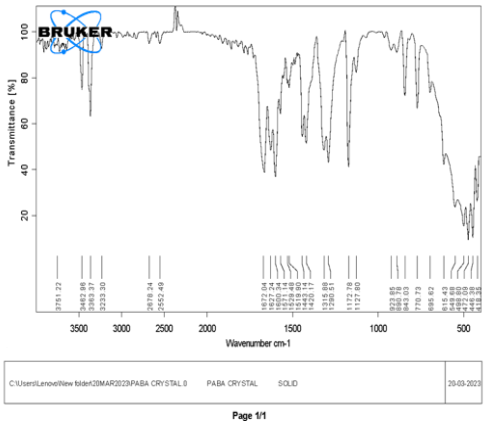


Figure 6: FTIR of cocrystals of Domperidone and Succinic acid

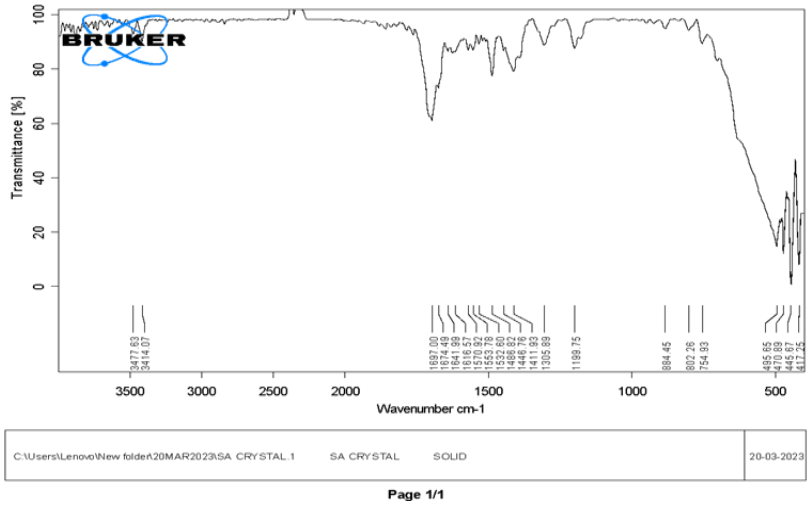
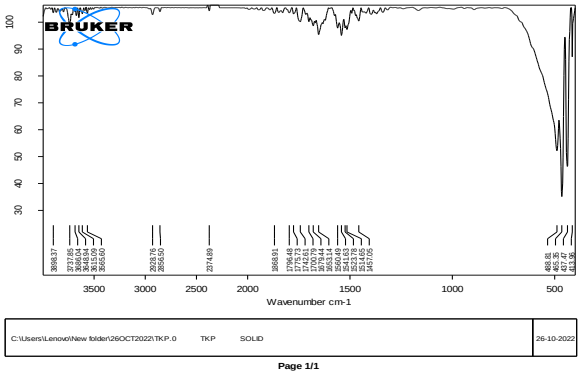


Figure 7: FTIR of Tamarind kernel powder



FTIR spectrum of sharp characteristic bands at 3125.18, 1694, 1486.33, 1382.68 and 1150 cm−1 due to stretching vibration bands of C=O, N-H, C-N, and two C-O respectively. The FT-IR spectrum of Domperidone showed a strong C=O stretch band around 1683.95 cm^{-1} and CO-NH stretching at 3072.26 cm^{-1}. FTIR spectrum of succinic acid showed a strong peak at 1201 cm−1 is a characteristic peak of dicarboxylic acid. The prepared co-crystal shows absence of CO-NH at 3072.26 cm^{-1} and shifting of characteristic peak 1683.06 cm−1 of amide to 1693.27 cm^{-1} in crystal form In SA crystal graph. It indicates the formation of crystal forms by carboxylic acid-amide heterosynthon. The CO-NH peak at 3072.26$cm^{-1}$of Domperidone disapper in the graph of cocrystal with para-amino benzoic acid indicates formation of bonding between drug and conformer. The broad absorption band in tamarind kernel powder at 3555.17 indicates the presence of -OH functional group. These can prove the theoretical chemical structure of tamarind seed consists of polysaccharide polymers of glucose, xylose and galactose. These structures are known to be responsible for the presence of -OH functional group in tamarind seeds. The spectrum of carboxylic acid represented by two absorption band. The first band is at the peak 1523.66 cm−1 with a C-O stretching vibration and the second band is 1679.03 cm−1 with C=O stretching vibrations. A sharp band occurs at peak of 2928.04 cm−1 because of the C-H stretching vibrations. These functional groups contain properties that can induced the process of coagulations for tamarind seeds.

Muco-adhesive strength:

Table 3: Force of adhesion and bond strength of tamarind kernel powder

Force of adhesion(N)	0.49
Bond strength(N-m^{-2})	0.102

The values of force of adhesion and bond strength indicates the tamarind kernel powder has sufficient mucoadhesive properties.

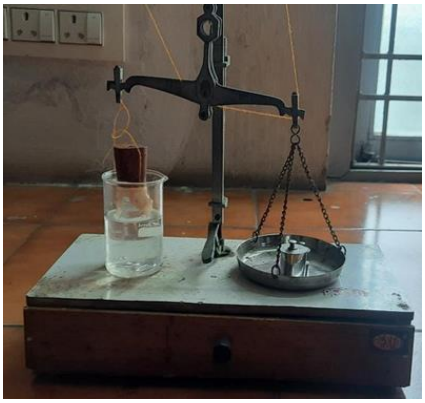


Figure 8: Modified physical balance method for measuring mucoadhesive strength of tamarind kernel powder

Table 4: Construction of standard graph of Domperidone:

	Absorbance values		
Concentration (µg/ml)	water	pH buffer 6.8	pH buffer 7.4
10	0.1996	0.1520	0.1630
20	0.2132	0.2338	0.2386
40	0.4648	0.4668	0.4927
60	0.6868	0.6550	0.6093
80	0.8625	0.8797	0.8101
100	0.9835	0.9623	0.9814

Figure 9: standard graph of domperidone in water

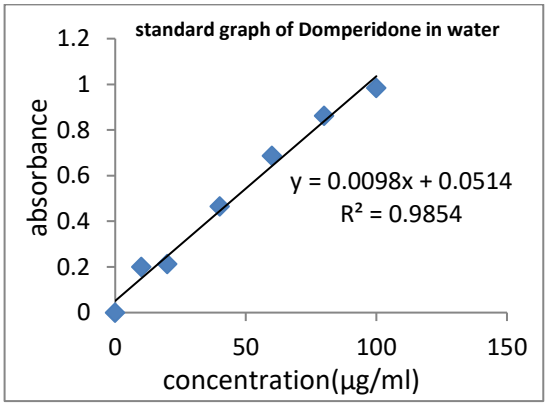
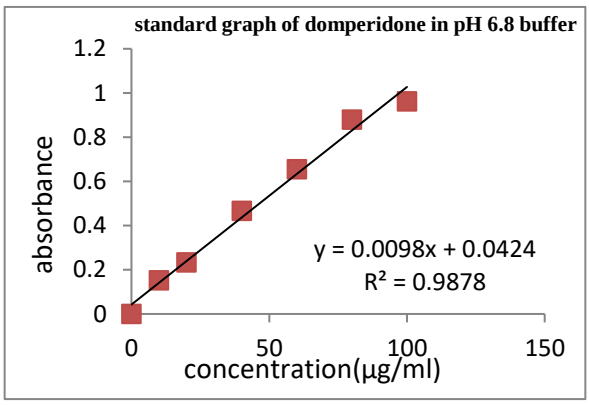


Figure 10: standard graph of domperidone in pH 6.8 buffer



In the standard graph the increase in concentration increases absorbance. Standard graph was constructed using UV spectrophotometry at lambda max of 284nm. The graph has linear relationship between concentration and absorbance with correlation coefficient values of 0.985 in water 0.987 in pH6.8 phosphate buffer.

Table 5: Solubility enhancement ratio

Formulation	Solubility enhancement ratio
PDBF1	39.54
PDBF2	48.78
SDBF1	67.86
SDBF2	83.76

Solubility gets enhanced by co crystallization there is 48.73 fold increase in aqueous solubility with paraamino benzoic acid and 83.76fold increase with succinic acid.

Table 6: Melting Point Values

	Original	Acquired
Pure Drug	200C	190^{0}C
Paba	187C	165^{0}C
Paba co-former	-	100^{0}C
Succinic acid	185C	170^{0}C
Succinic acid co-former	-	15 ^{o}C

The change in melting point from the pure compounds (drug and coformers) indicate the formation of cocrystals.

Table 7: Evaluation of buccal films

Formulation	Folding endurance	Drug content	Swelling index	Surface pH
PDBF1	190.6	63%	1.1	6.67
PDBF2	181.8	72%	0.75	6.66
SDBF1	156.4	80%	2.1	6.68
SDBF2	126.3	82%	1.1	6.73

The folding endurance of all the four formulations ensures sufficient mechanical strength for the films and drug content values were in the range of 63-82%, sufficient swelling index and pH values wihin the range.

In vitro diffusion studies:

Figure 11: Zeroorder graph

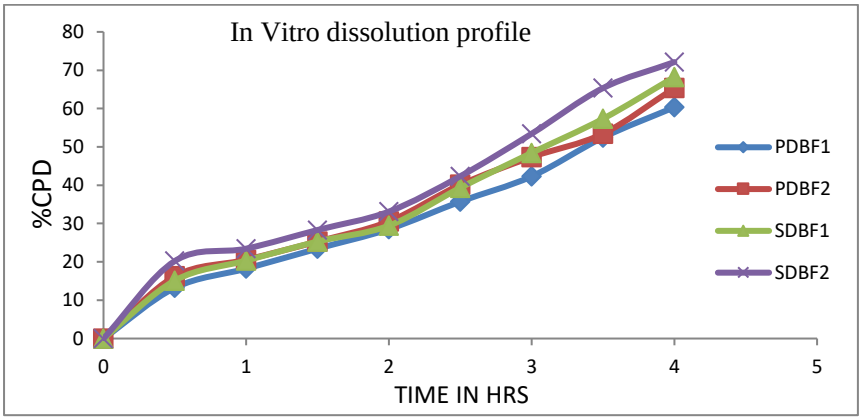


Figure 12: First order graph

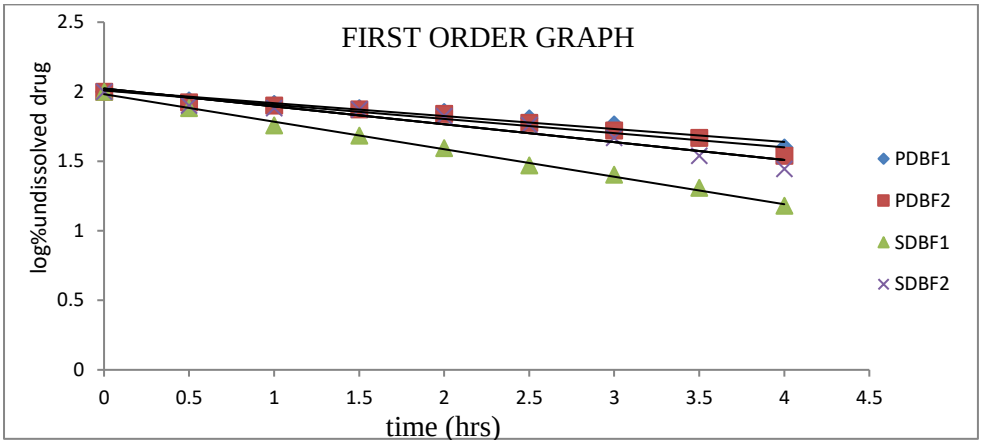


Figure 13: Higuchi graph

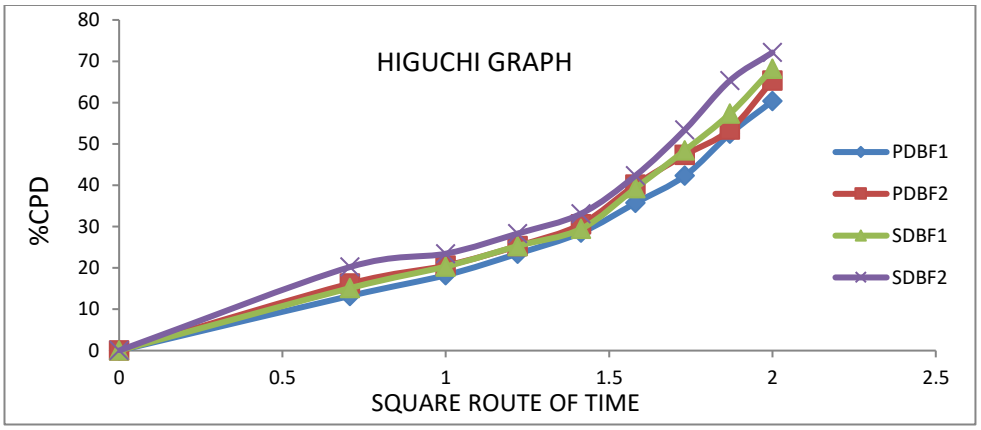


Figure 14: korsemeyer peppas graph

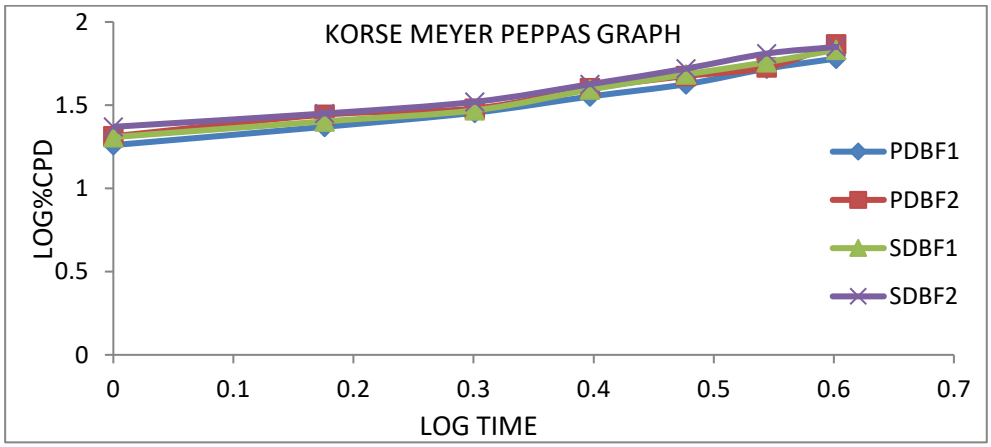


Table 8: correlation coefficient values and n values of korsemeyer peppas graph

	r^2 values			
Formulation	Zero order	First order	Higuchi Graph	Korsemeyer n values
PDBF1	0.9486	0.9454	0.9365	0.2315
PDBF2	0.9541	0.9364	0.9295	0.2672
SDBF1	0.9825	0.9968	0.9676	0.3497
SDBF2	0.9705	0.9915	0.9543	0.3683

Based on the r^2 values the drug release follows first order that is the drug release depends on the concentration. The drug release is follows diffusion mechanism and as n values of korsemeyer peppas graph indicates the drug release is case 1 fickian diffusion. Based on diffusion studies the SDBF2 has shown 86% drug release in 4hrs and has concluded as optimized formula.

CONCLUSION

The solubility of domperidone gets enhanced by crystallization with para amino benzoic acid and succinic acid. The prepared buccal films have sufficient strength, pH and swelling index and in-vitro diffusion studies has shown that the buccal films prepared with domperidone with succinic acid 1:2 ratio has shown better drug release and it was the optimized formula. the work has also concluded that the tamarind kernel powder has sufficient muco adhesive strength and can be used as mucoadhesive polymer in novel formulations

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References

1. Peltonen L, Practical guidelines for characterization and quality control of pure drug nano particles and nano-crystals in the pharmaceutical industry, Advanced drug delivery rev, 2018;13(1):101-115. https://doi.org/10.1016/j.addr.2018.06.009 PMid:29920294

2. Sarfaraz Md, Sushil Kumar, Doddayya H, Fabrication and evaluation of mouth-dissolving films of domperidone, International Journal of Current Pharmaceutical research, 2023;15(2): 36-43. https://doi.org/10.22159/ijcpr.2023v15i2.2088

3.Thorat KV, Khade P, Kakade S,Bhosale A, Formulation and evaluation of fast dissolving mouth film of domperdone, World Journal of Pharmaceutical sciences,2021;10(12) :2104-2121.

4. Khobragade DS, Goud UB, Prakash JSV, Pranav Kumar A.V.R, Reddy GRS, Potbhre M, Formulation and evaluation of polymer based, rapid onset, patient friendly, oral film of Domperidone maleate, World Journal of Pharmaceutical sciences , 2016; 4(1): 115-122.

5. chawanorasest K, saengtongdee P, kaemchantuek P, Extraction and characterization of Tamarind (Tamarind indica L.) Seed polysaccharides from three different sources, molecules, 2016 ;21(6): 775. https://doi.org/10.3390/molecules21060775 PMid:27314322 PMCid:PMC6274079

6. Pandekal MS, Tegginmat PK, Formulation and evaluation of bioadhesive patch for buccal delivery of Tizanidine, Acta pharmaceutica sinica B, 2012;2(3): 318-324. https://doi.org/10.1016/j.apsb.2011.12.012

7. Jassim ZE, Al-Kinani KK, Alwan ZS, Preparation and evaluation Pharmaceutical Cocrystals for Solubility Enhancement of Dextromethorphan HBr, International journal of drug delivery and technology,2021;11(4):1342-1349.

8. Dhakar RC, Maurya SD, Sagar BPS, Bhagat S, Prajapati SK, Jain CP, Variables influencing the drug entrapment efficiency of microspheres: A pharmaceutical review, Der Pharmacia Lettre, 2010;2(5):102-116

9. Natevschul thesis, Jan-dav henck. Role of co crystals in the pharmaceutical development continuum. In:Wouters J, Quere L, editors. Pharmaceutical salts and co-crystals. Cambridge: The royal society of chemistry; 2012.p.110-125. https://doi.org/10.1039/9781849733502-00110

10.Brittain HG. Co-crystals systems of pharmaceutical interest, Cryst growth des 2012;12(2):1046-54. https://doi.org/10.1021/cg201510n

11. Blagden N, de Matas M. Gavan PT, York, P crystal engineering of active pharmaceutical ingredients to improve solubility and dissolution rates, Advanced Drug delivery Revison ,2007;59(7):617-630. https://doi.org/10.1016/j.addr.2007.05.011 PMid:17597252

12. Izutsu KI Koide T, Takata N, Ikeda Y, Ono M and Inoue M, Characterization and quality control of pharmaceutical co-crystals, Chemical and pharmaceutical bulletin, 2016 ;64(10):1421-1430. https://doi.org/10.1248/cpb.c16-00233 PMid:27319284

13. Douroumis, D, Ross SA, Nokhodchi A, Advanced methodologies for co-crystal synthesis. Advanced drug delivery Reviews, 2017;11(7):178-95. https://doi.org/10.1016/j.addr.2017.07.008 PMid:28712924

14. Stoler E. Warner JC, Non-covalent derivatives co-crystals and eutectics molecules 2015:20(8);14833-48. https://doi.org/10.3390/molecules200814833 PMid:26287141 PMCid:PMC6332263

15. Kotak U, Prajapati VD, Solanki HK , Jani GK Jha p, Co crystallization tech its rationale and recent progress, world Journal of Pharmaceutical sciences, 2015;(2):484-508 .

16. Aboutaleb A.E., Abdel-Rahman S.I., Ahmed M.O, Younis M.A, Design and evaluation of domperidone sublingual tablets, International journal of Pharmaceutical . Sciences, 2016;8:195-201.

17. Ali M.S., Vijendar C., Sudheer Kumar C., Krishnaveni J, Formulation and evaluation of fast dissolving oral films of diazepam. Journal of Pharmacovigiance,2016;4(3):1000210. https://doi.org/10.4172/2329-6887.1000210

18. Alim M., Karna S., Chaturvedi S, Agrawal V.K, Validated UV spectrophotometric method for estimation of domperidone for dissolution study, Der Pharmacia Lettre,. 2015;7:53-58.

19. Alipour S., Akbari S., Ahmadi F, Development and in vitro evaluation of fast-dissolving oral films of ondansetron hydrochloride, Trends in Pharmacological sciences, 2015;1:25-30

20. Almeida N.M.G., Lima R, Alves T.F.R, Rebelo M.A, Severino P, Chaud M.V,A novel dosage form for buccal administration of bupropion, Brazilian Journal of Pharmaceutical Sciences, 2015;51:91-100. https://doi.org/10.1590/S1984-82502015000100010

21. Arya A, Chandra A, Sharma V, Pathak K, Fast dissolving oral films an innovative drug delivery system and dosage form, International. Journal of ChemTech Research, 2010;2:576-583

22. Tong X, Pan W, Su T, et al, 2020. Recent advances in natural polymer-based drug delivery systems, Reactive & FunctionalPolymers,148;104501. https://doi.org/10.1016/j.reactfunctpolym.2020.104501

23. Kumar GA, Wadood SA, Maurya SD, Ramchand D, Interpenetrating polymeric network hydrogel for stomach-specific drug delivery of clarithromycin: Preparation and evaluation, Asian Journal of Pharmaceutics-October-December 2010; 179-184 https://doi.org/10.4103/0973-8398.76738

24. Prasanthi N, Krishna CS, Gupta ME, Manikiran SS, Rama Rao N. "Design and Development of Sublingual Fast Dissolving Films for an Antiasthmatic Drug, Scholars Research Library, 2011.

25. Goel H, Rai P, Rana V, Ashok K Tiwary K, Orally disintegrting systems: Innovations in formulation and technology, Recent patents on drugdelivery and formulation, 2008; 2(3) : 258-274. https://doi.org/10.2174/187221108786241660 PMid:19075912

26. Srujana S, Anjamma M, Alimuddin, Singh B, Dhakar RC, Natarajan S, Hechhu R. A Comprehensive Study on the Synthesis and Characterization of TiO2 Nanoparticles Using Aloe vera Plant Extract and Their Photocatalytic Activity against MB Dye. Adsorption Science & Technology. 2022;2022 https://doi.org/10.1155/2022/7244006

27. Arya A, Chandra A, Sharma V, Pathak K. Fast Dissolving Oral Films: An Innovative Drug delivery System and dosage Form, International Journal of ChemTech Research, 2010;2: 576-583.

28. Apoorva M, Neha C, Geeta A, Formulation and characterization of fast dissolving buccal films: a review, Der Pharmacia Lettre, 2011; 3(1):152-165.