Formulation, Evaluation And Enhancing the Solubility of Orodispersible Tablets of BuclizineHcl.

Dr. Nepram Swarnalata
Selection Grade Lecturer in Govt.PolytechnicImphal Manipur
nepramswarnalata@yahoo.co.in

***Abstract*— Drugs have been developed and delivered in patient different delivery system . Among the various dosage forms, tablets taken orally are considered to be the most convenient and stable unit doses forms. But the geriatrics bed ridden, psychotic's patients travelers and pediatrics find difficulty in swallowing the conventional dosages forms like tablets, capsules etc. Due to dysphagia this problems results in not taking the prescribed medication properly and have the efficacy of treatment being severely affected (Seager*etal* 1988) Being aware of these problems and to fulfill the medical needs, a segment of formulation better known by the phrase Orodispersible tablets (ODTS) has been developed by (Dobetti*et al* 2001, Schiermeier*et al* 2002) Buclizine, 1-(4-tert-butylbenzyl)-4(4-chlorobenzhydryl) is a piperazine derivative having antiemetic, antihistaminic, antimuscaranic, and selective properties used in motion**

In development of ODT formulation of buclizineHCl the problem faced was with its solubility and there by affecting the release profile .So an attempt has been made to increase the solubility of BuclizineHCl by complexing with Betacyclodextrin, the optimised ratio of superdisintegrants and other suitable polymers.in 1:1 molar ratio by kneading method formulating this complex of buclizineHCl and beta-cyclodextrin along with optimized polymers and excipients by direct compression method and evaluated .It showed desired characteristics of ODTS and maximum release profile.

INTRODUCTION

Among the various dosage forms, tablets taken orally are considered to be the most convenient and stable unit doses forms. But the geriatrics bed ridden, psychotic's patients travelers and pediatrics find difficulty in swallowing the conventional dosages forms like tablets, capsules etc. Due to dysphagia this problems results in not taking the prescribed medication properly and have the efficacy of treatment being severely affected **(Seager*etal* 1988**).Being aware of these problems and to fulfill the medical needs, a segment of formulation better known by the phrase Orodispersible tablets (ODTS) has been developed by **Dobetti*et al* 2001, Schiermeier*et al* 2002**.

This is an innovative dosage form that disintegrates in mouth upon contact with saliva in less than 60 second forming a suspension which is easy to swallow without intake of water. Many inventors, companies, regulatory agencies and official references have mentioned various synonyms to these mouth dissolving tablets, as orally disintegrating tablets, rapid-melt, melt in mouth tablets. Fast dispersing so on so fast in orange book **CDER** (center for drug evaluation and research) defines ODT as a solid dosage form containing active pharmaceutical ingredients which disintegrates rapidly within seconds when placed in tongue (**CDER 2007**). **The European pharmacopoeia 2006** recognizes mouth dissolving tablets as orodispersible tablets (ODTS).

The objective of the present study is to develop orodispersible tablets (ODTS) of buclizineHCl by using suitable polymer to meet the desired characteristics of ODTS and optimize the most appropriate formulation and across the optimized formulation for its *in-vitro* release profile consistency.

In development of ODT formulation of buclizineHCl the problem faced was with its solubility and there by affecting the release profile bioavailability.The study aims in enhancing the solubility of buclizineHCl by complexing it with beta-cyoclodextrin in 1:1 molar ratio by kneading method formulating this complex of buclizineHCl and beta-cyclodextrin in orodespersible tablets (ODTS) by adding optimized ratio of superdisintegrant (ie,crospovidone), fillers, microcrystalline aerosil, sweetening and flavoring agents by direct compression method were evaluated and studied. Its *in-vitro* release profile. And it showed the desired characteristics of ODTS and maximum release profile.

MATERIAL AND METHODS

Buclizine hydrochloride was obtained as a gift sample from UCB India pvt limited Mumbai. Buclizine hydrochloride conventional tablets in brand name of longefene was purchased from retailed shop. Beta cyclodextrin was purchased from Sigma Aldrich (St Louis, MO). Ac-Di-Sol (Croscarmellose Sodium, Kawarlal and Sons Chennai, India).Crospovidone, Nanhang Industries Co Ltd Zhoupu, China), Primogel (Sodium starch glycolate) were used as super disintegrantsAerosil 200(Silicon Dioxide Kawarlal and Sons Chennai, India)

Microcrystalline cellulose cyclocel 101 and 102 (Wei Ming Pharmaceutical Mfg Co Ltd China), Hydroxy propyl methyl cellulose(M.K scientific New Delhi). Lactose monohydrate, Magnesium stearate CDH Pvt Ltd New Delhi was used as filler and lubricants. Aspartame, vanilla flavours, (Kawarlal and Sons Chennai India) All others reagents and solvents used were of analytical and pharmaceutical grade.

Preformulation studies:**-1. Standardization of the drug sampe**The drug sample of buclizine hydrochloride was authenticated as per official pharmacopoeias (**British pharmacopoeia2008**) and **Martindale West cott 1996**)

Physical standardization of buclizine hydrochloride:-

Buclizinehcl sample were evaluated for physical appearance, odor solubility in various solvents and melting point.

SOLUBILITY

Table 1. Shows solubility of drug sample buclizine hydrochloride.

S. no	Solvent	Solubility
1	Water	Insoluble
2	Chloroform	Sparingly soluble
3	Ethanol	Slightly soluble
4	Methanol	Freely soluble

FTIR ANALYSIS: FTIR analysis was done on a FTIR spectrometer; 5mg of the drug substance was weighed. It was thoroughly triturated with 95 mg of potassium bromide .A pallet was made out of the mix and introduced into the instrument in pallet sampling compartment. The spectrum was recorded from 400 to 4000/cm at the ambient temperature.

PREPARATION OF STANDARD CURVE

Preparation of Stock Solution of Buclizine –hydrochloride Stock solution of BCZ-HCl was prepared by dissolving 10 mgs of drug in 100ml 0f solvent (100µgm/ml).

PREPARATION OF STANDARD CURVE OF BUCLIZINE HYDROCHLORIDE IN 0.1N HCL

. A calibration curve was obtained by measuring the absorbance at λ_{max} of 230 nm against blank. The readings were recorded in triplicate and the experiment was repeated on three consecutive days using freshly prepared stock solution each time.Value of absorbance was plotted against the concentration. Since we are formulating orodispersible tablets so standard curve was plotted in simulated saliva (Gal *et al 2001).*

COMPATABILITY STUDIES

Drug and polymers interactions and compatibilities studies were done by DCS differential scanning colorimeters (Perkin –Elmer DSC-7), FTIR .

Drug release studies :- by dissolution studies and sample were analysed by using double beam uv spectrophotometer.

Formulation of ODT BUCLIZINE HYDROCHLORIDE(BCZ HCL) which is Biopharmaceutical classification system BCS11 is poorly soluble drug . Initially the required dose was directly prepared by compressing the ingradients containing the microcrystalline (avicel 102) aerosol and other ingredients fillers; lubricants flavouring agents. sweetening agents .However, ***in-vitro*** dissolution studies showed that orodispersible tablets did not release the drug completely. The problem was overcome later by forming 1:1BCZ HCl , BCD complex.

Preliminary Studies

Characterisation of complexes

Thermal behavior of BCZ HCl were examined X-ray diffraction studies (XRD) were performed to study the physical mixture by using X-ray Model no. DY2020 X"PERRT pan analytical Netherland.

FTIR AND SEM (Scanning electron microscope)

Photomicrograph of pure drug and the complex in molar ratio 1:1 were taken at 10.00 kx magnifications using SEM ZEISS EVO-50 Germany.

Dissolution studies were carried out for the complex also and compared with the marketed product LONGEFENE UCB Pvt. Limited. And stability studies carried out as per ICH guideline.

Table 2 :-showing formulation of Orodispersible tablets of BCZ HCL

Average weights of each tablet of all formulation are kept at 200 mg.

Code	Drug	HPMC	MCC	Asp	fla	Mgst	ccs	lac	Aero
A0	25	10	50	3	1	1	0	106	4
A1	25	10	50	3	1	1	4	102	4
A2	25	10	50	3	1	1	6	100	4
A3	25	10	50	3	1	1	8	98	4
A4	25	10	50	3	1	1	10	96	4
A5	25	10	50	3	1	1	12	94	4
A6	25	10	50	3	1	1	14	92	4

Drug -BuclizineHCl
HPMC-Hydroxy propyl methyl cellulose
MCC -Microcrystalline cellulose
Asp -Aspartame Sweetning agent
Fla - Flavouring agent
Mgst- Magnessium stearate
Ccs - Croscarmellose sodium
Lac- lactose
Aero – Aerosil

Table 3 shows the composition of tablets formed by complexation with beta cyclodextrin.

Drug complex	HPMC	MCC	Mgst	asp	fla	ccs	lac	Aero	TOTAL
81.25	10	50	1	3	1	6	43.75	4	200

All the above given values are in milligrams showing formulation for one tablet.

Drug complex: -BuclizineHCl and betacyclodextrin 1:1 molar ratio.

Physical evaluation of ODTs of BCZ &BCD complex

In physical parameter, all the batches were evaluated for weight variations, hardness, disintegrating time appearance, friability and wetting time.

Phase Solubility Study

Solubility studies were performed according to the method described by Higuchi&Connors. An excess amount of buclizineHCl was placed in different concentrations of betacyclodextrin.

The contents of the flask were equilibrated by shaking for 72 hrs in thermostatically controlled water bath at 25°C. After attainmentof equilibrium the content of each flask was then filtered.The filtrate was then assayed spectrophotometrically for BuclizineHCl at 222nm using UV spectrophotometer (Shimadzu, KOITO, Japan)

DISSOLUTION STUDIES OF COMPLEX

Dissolution test were performed in triplicate with USP apparatus-2 (VEEGO- VDA 80 India) at temperature 37°C and paddle method at 50 rpm.

0.1N HCl is used as a dissolution media. Volume of media is 1000ml.

Sampling done at time interval 2, 5, 10, 15, 20, 25, 30 mins and filtered and dilution done appropriately. The samples

were studied spectrophotometry at 222nm and percent of cumulative release was calculated.

COMPARISON WITH MARKETED BRAND

The dissolution of complex drug was compared with marketed brand of buclizine hydrochloride (Longifene) UCB Pvt Ltd. INDIA

STABILITY STUDIES

The stability studies of optimized batch were subjected to stability studies as prescribed in ICH (International Conference on Harmonization) guide lines. Article QIA (R2) which mentions the guideline of stability testing of new drug substances and products, modules selected was intermediate and accelerated stability studies of as per ICH guideline.

Tablets from the optimized batch were kept at intermediate stability conditions of 30°C ±2°C 65%RH ±5 RH and accelerated stability condition of 40°C ±2°C,75% ± 5%RH for six months. The humidity was attained by keeping a supersaturated solution of sodium chloride and sodium nitrite respectively for 75% and 65 %RH respectively in the desiccators. The tablets were packed by first wrapping in thin plastic sheet and then in aluminium foil, kept in the desiccators. The desiccators were placed in control temperature incubators. The stability samples were subjected to *in-vitro* analysis, FTIR and DSC after 0,3,6 month variations observed. If no significant changes then the product formulated is stable.

Result and Discussion

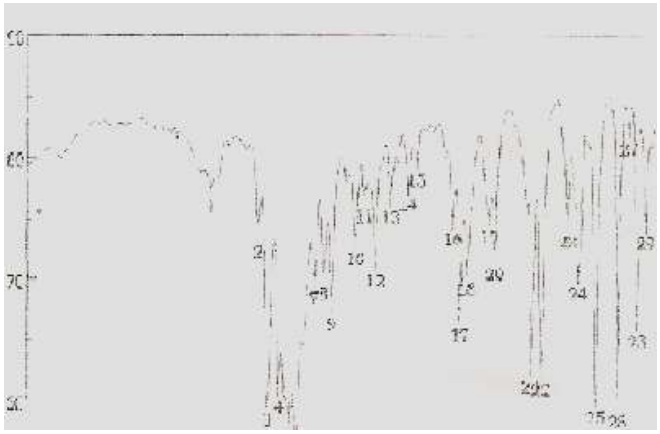


FIG 1 SHOWS THE FTIR PEAK

Peaks were compared with standard BuclizineHCl**Clark's analysis of drug and poisons**
3rd edition 2nd volume page no 715

Principle peak at wavelength 1002cm^{-1}, 1131cm^{-1},754cm^{-1},800cm^{-1}, 1075cm^{-1}.

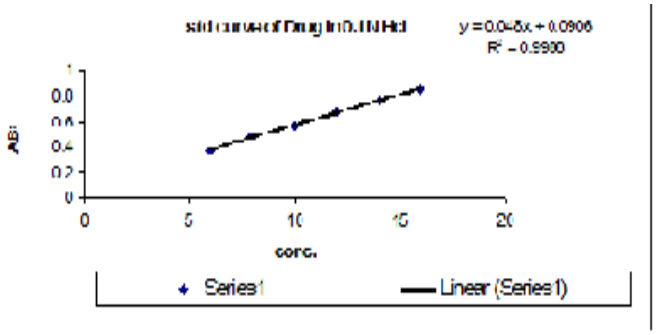


Fig 2 Standard Curve In Simulated Saliva:

Standard curve was prepared by plotting absorbance against different concentrations of drug solution in simulated saliva PH 6.8.The equation obtained was linear with a regression coefficient of 1.

Standard curve of buclizine Hydrochloride have shown the linear relation between concentrations and Absorbance (follows Beer Lambert "s law), these equations can be used to calculate unknown Concentration of drug when absorbance is known in respective media.

DRUG POLYMER INTERACTION STUDIES

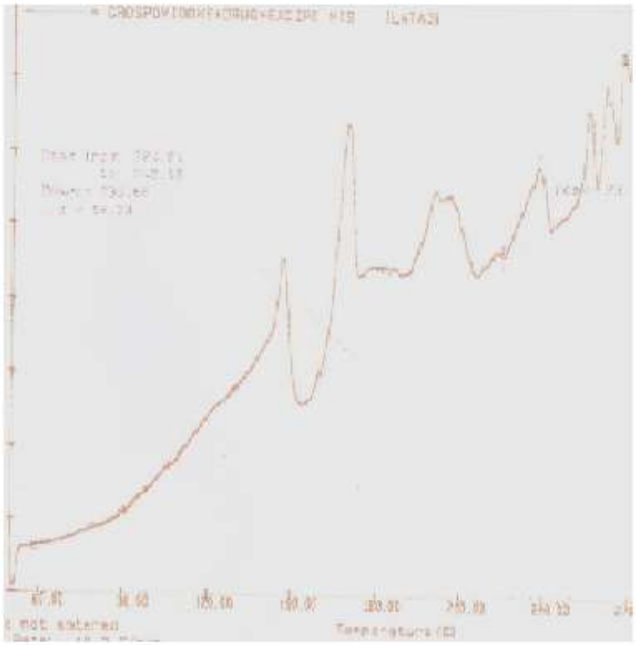


FIG 3 SHOWS THE DSC OF DRUG WITH CROSPOVIDONE AND OTHER EXCIPIENTS

DSC shows that endothermic peak of drug in physical mixture of drug with crospovidone and other excipients was found to be 237.21

DSC analysis of drug with excipients shows that endothermic peak of drug remains within limits. No significant shifts in endothermic peak were found in physical mixture of drug and excipients as compared with the pure drug which was found to be at 238.25.°
Therefore the drug and excipients are compatible in formulation.

EVALUATIONS OF FORMULATIONS

- Physical parameters of formulation

All the batches of the formulation were evaluated for weight variation, hardness, Disintegration time thickness wetting time,

	Weight	Hardness kg/cm²	Disintegration Time(Sec)	Wetting time	Friability
A0	201.1±0.22	5.9±0.18	120 ±0.10	24.60+ 0.52	3.33±0.1
A1	205.6±0.65	5.2±0.15	35±0.21	14.53+ 1.84	3.49±0.4
A2	200.5±0.98	5.5±0.12	26±1.2	8.64+ 1.62	3.43±0.1
A3	203.5±0.98	4.5±0.08	23±5.2	8.50+ 1.02	3.52±0.5
A4	202.7±0.98	4.0±0.03	8 ±5.2	7.8+ 1.3	3.54±0.2
A5	200.9±2.15	2.8±0.03	9 ±1.90	7.5+ 0.99	3.55±0.4
A6	204.5±2.08	1.0±0.1	5 ±0.25	7.0+ 1.35	3.56±0.3

:-.Disintegration time of A0 is more than 3mins and hence it does not fulfill the requirement characteristics of ODTs A3, A4, A5, A6 shows a good disintegration time but they cannot withstand the rigors of manufacturing process and handling due to insufficient strength.In addition ,tablet should be able to withstand reasonable abuse when in hands of consumer such as bouncing about in woman ;s purse. Adequate tablet hardness and resistance to powdering and friability are necessary for consumer acceptance.conventional compressed tablets that lose less than 0.5 to1.0% of their weight are generally considered acceptable

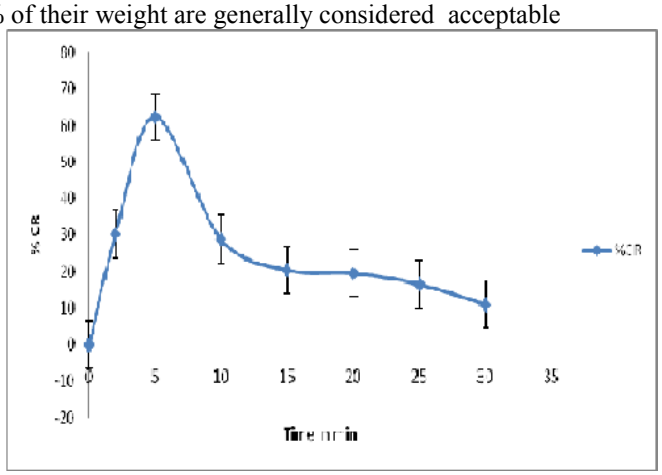
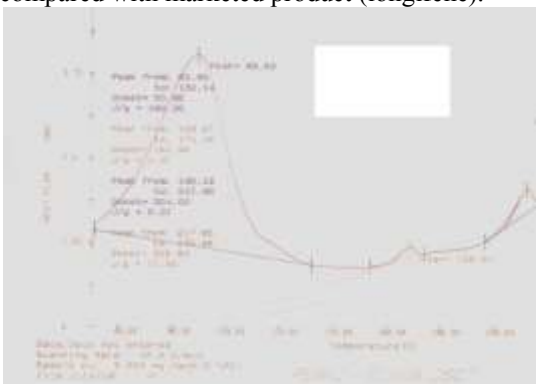


FIG 4 SHOWS THE RELEASE OF BATCH A1

Result:- The maximum release was 62.32% in 5 mins. in batch A1

As the concentration of disintegrant goes increasing the hardness decreases and it cannot withstand the rigors of manufacture and shipment. Hence batch A4 ,A5 A6 were not considered. Considering the release profile of A2 the release of the drug was maximum in five mins in all the batches hence it can be inferred that we can formulate the orodispersible tablet with these polymers and excipients but its release is less than 80% hence its absorption and bioavailability will be erratic. We can bring a good release by enhancing the solubility of the drug buclizine hydrochloride by complexing with the beta cyclodextrin.
Complexation is done in molar ratio 1:1 by kneading method .And following are the results of characterization performed; the complexes were stable. . Formulated ODTs by using this complex , crospovidone 3% (optimized conc of disintegrant)and other polymers and release profile of the formulated ODT were studied as given below and is compared with marketed product (longifene).



There is a shift in the endothermic peak of the drug and that of complexing agent betacyclodextrin indicating reduction in drug crystallinity due to complexation. The peak for drug before complexing was 238.25°C and it has come down to 212 °C and the endothermic peak of beta cyclodextrin disappeared and a new peak with different shape appeared at 89.63°C which can be attributed to the formation of an inclusion complex. .

These shifts in peak shows that there is complex formation

FIG 5 FT-IR OF THE BCZ AND BCD COMPLEX

FIG 6. SHOWS THE SEM OF PURE DRUG BUCLIZINE HYDROCHLORIDE

SEM is to assess the microscopic aspects of the drug, the complexing agent, and the complexes formed. Although this method is not conclusive method to confirmed complex formation . Pure BuclizineHCl is characterized by the presence of a crystalline particles of regular size.Purebetacyclodxrin also appear in crystalline form.

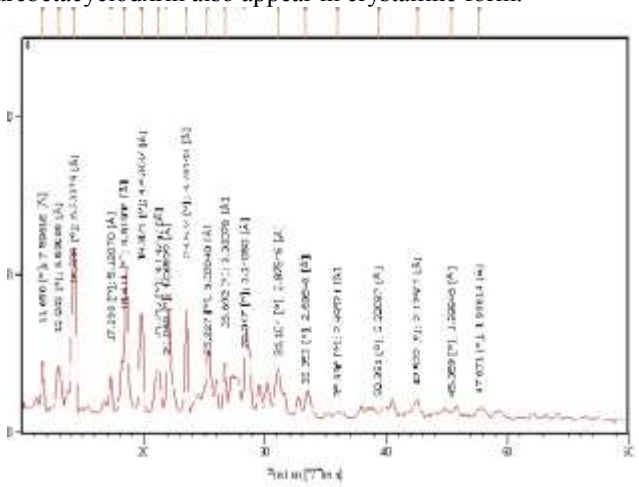


Fig 7 shows the XRD Patternshows the x-ray diffraction pattern of the drug crystalinity was determined by comparing some respective peak heights in the diffraction patterns of the binary system with those of a reference.

As a consequence of the coincidence of diffraction peaks between buclizine and beta-cyclodextrin characteristics peaks of buclizineHCl situated at 0 °and 40° (2θ) were used for confirmation studies. The complexes show all characteristics peaks corresponding to the drugs, but with lower intensity concentration and possible reduction in crystallinity due to complex formationAfter the characterization of complex. Formulated ODT of the complex with other excipients

And release profile is studied.

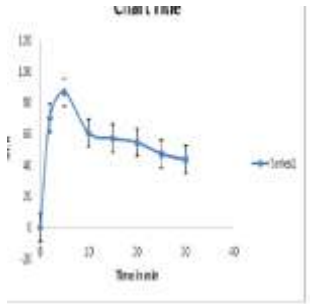


FIG .8 shows the release profile of ODT formulated by complexation with beta-Cyclodextrin

There is enhancement in dissolution profile due to the formation of inclusion complexes and reduction in crystallinity of the product as confirmed by X-ray diffraction study. The release is 86.58 % in five minutes which is the maximum compared to all the formulations.The marketed product shows a release of 77.6% in 45 minutes. Hence one has to take the drug 30 mins before traveling to control the emetic episode.

Buclizine hydrochloride in ODT form will give immediate action because of its rapid disintegration and good release within five minutes. And it highly patient compliance since it can be taken without water.

CONCLUSION

BuclizineHCl as orodispersible tablet and optimized formula was subjected to physico-chemical and pharmacokinetic evaluations.

Technique of direct compression of drug with compressible excipients like MCC , aerosol and superdisintegrantcrospovidone ,crosscarmellose in different ratio were added to formulate the ODTs and give taste palatable and disintegrates in less than 30 seconds.

It is being found that drug BCZ HCl is compatible with HPMC,crospovidone,MCC,Lactose,crosscarmellose in the formulation. It was shown by DSC &FTIR studies.

Hardness , wetting time,disintegrating time of tablet containing crospovidone show promising result and hence it is selected for preparation of the ODTs (orodispersible tablets).Since the drug BCZHCl is practically insoluble in water hence its dissolution profile was poor. Hence the drug is complexed with beta-cyclodextrin in molar ratio 1:1 by kneading method. Complexation was characterized by DSC ,FTIR, & SEM. Results reveal that complexation result in increase of solubility and dissolution rate for the drug suggesting a possible enhancement of its oral bioavailability. Dissolution profile of the orodispersible tablet (formed by complexation) shows a fast release nearly 86.5%in gastric PH (1.2) in first five minutes in *in-vitro* conditions**.**

Comparision of dissolution profile of the optimized tablets (3%crospovidone) and marketed product (Longifene). The optimized formulation shows the burst release at 5 mins whereas the marketed product shows its maximum release of 77.6% at 45 minutes. Hence it is to be taken 30 mins before traveling.

Stability studies DSC thermograms of the optimized table has confirmed the stability of the drug molecule in the tablet form after intermediate and accelerated storage condition.

On the basis of above conclusion BCZ HCl at dose 25 mg can be formulated as orodispersible tablets (ODTs) by direct compression method solubility is enhanced by complexing with beta cyclodextrin and this method is simple, reliable and cost effective,without any liquid intake.Finally it can be concluded that ODTs of BCZ HCl was ideal for geriatric pediatric and travelers consuming tablet in supine position intake of liquid. This formulation is highly patient compliant and should be tried with other drug candidates.

Acknowledgement

The author would like to thank heartily to DrShailendra,Sharma Associate Prof. Faculty of Pharmaceutical sciences Jodhpur national University jodhpur for his guidance and inspiring me to carry out research work.

K.Bhanumati Devi, HOD Pharmacy dept.

Govt. Polytechnic TakyelImphal. Manipur for her guidence and motivation

Sir M.Ibomcha Singh

Controller technical education for motivating me to persue the research work

Sir R.K.Nando

Principal, Govt.PolytechnicTakyel.Imphal
For motivating me giving me moral support.

REFERENCES

[1] Abdelbary, G Eouani, C.Prinderre, P. Reyneir J (2005). Determination of the invitro disintegration profile of rapidly disintegrating tablets and co- relation with oral disintegration.

[2] ArunRasheed, Ashok Kumar, C.K.Sravanthi V.V N.S.S J (2008) Scipharm .at. Cyclodextrin as drug carrier molecules a review.

[3] Aqualon Klucel (2004) Technical literature (2004), Hydr oxy propyl methycellulose application in a sustained release matrix capsule dosage form

[4] Baoota .S Dhaliwal M, Kohli K, (2004) J AAPS Pharm SciTech 06 (01) E 83-90.Physicochemical characterization in vitro dissolution behavior and pharmacodynamicstidies of Rofecoxib – cyclodextrin inclusion compounds.

[5] Bedine,M.S.,Bayless, T.M (19 73) J Gastroentology.65, p-735-743 Intolerance of small amounts of lactose by individuals with low lactase level

[6] Bi et al (1996) Pharm .Chem. Bull 44,p-2121-2127 Preparation and evaluation of a compressed tablets rapidly disintegrating in the oral cavity.

[7] Bi Y (1996) J Chem. Pharma bull 44 p- 2121-2127 Preparation & evaluation of a compressed tablets rapidly disintegrating in the oral cavity.

[8] British pharmacopoeia (2003) The stationary office under licenses from the controller of her Majesty‘s stationary office for the department of health on behalf of the health minister p- 272.

[9] Chang,R.K,Guo,X,BurnsideB.A,Couch R,A,2002. Fast dissolving tablets.J Pharm.Tech.24, 52-58

[10] C.Moriwaki, G.L Costa, C N Ferracine, F.F de Moraes,G.M-Zanin,E.A.G Pined &G.Matioli. J (2008) Brazilian journal of chemical engineering volume 25 . P-255-267.

[11] Enhancement ofsolubility of albandazole by complexation with beta- cyclodextrin.

[12] Dobetti, L(2001) Fast - melting tablets: development and technologies Pharma Technology Drug Deliv:44-45

[13] A.European pharmacopoeia (supplement 2001) 3rd edition, European Department for the quality of Medline, Strasbourg-1666-1669.

[14] A. Fang Zhang, Lei W, ZhiH.Zhan.T,Liu W.(2006) Value of mink vomit model in study of antiemetic drugs. W.J .Gastroenterology12, p-1300-1302.

[15] A. arhan Ahmed Siddiqui, Agha ZeeshanMirza, HashimZuberi. Faizaqureshi. J (Med chem. Research 2009) Optimisation of quantitative analysis of buclizine hydrochloride using U-V Spectrophotometry in bulk drug and dosage formulations.

[16] Gal, Jy (2001) About synthetic saliva for invitro studies Talanta 53:1103-1115.

[17] GarauravSwami,Koshy .M.K, ManishaPandey,Shubhini A. Saraf. (2010) International Journal of Advances in Pharmaceutical Sxiences. P. 68- 74.

[18] Preparation and characterization of domperidone beta cyclodextrin complexes prepared by kneading method.

[19] Gohel M.C (2005) A review of processed directly compressible excipients J. pharma. Sci 8(1) :76-93

[20] Haresh M. Patel, Bhanubhai, N. Suhagia, Shailesh, A Shah,Ishwar Singh Rathod Vijay K.Pasman. ( )JActaPharma 57 p-351-359 Preparation and characterization of etoricoxib –beta- cyclodextrin complexes prepared by kneading method.

[21] Higuchi T./ & Connors K .A Phase solubility techniques Adv. Analytical chemistry Instrumental 4(1965) p 117-212-

[22] Indurwade, N.H Rajyaguru ,T.H Nakhat (2002) J

[23] Novel approach- Fast Dissolving Tablets .Indian

[24] Drugs 39, 51

[25] Jaccard&Leyder J (1985) J Ann Pharm Fr 43: p-123-131. Une nouvelle formegalenique(pubmed)

[26] J.R.Moyano, J.M Gines. M,J.Arias, A,M.Robasco. International Journal of pharmaceutics (1995). 114 p-95-102

[27] Kamal Dua, M.V.RamanaU.V.Singh. Sara, M.Himaja, AbhinavAgarwal, VaibhavGarg and KavitaPabrija. Journal “Current Drug Delivery (2007) 4th edition p-21-25. Investigationof enhancement of solubility of norfloxacin beta cyclodextrin in presence of acidic solubility additives.

[28] Leon Lachman ,Herbert A.Liberman, JoshepL.Kanig (1990) 3rd edition p- 185

[29] LoftssonT,GuommundSdotterJ.Sigurjonsdottir,J.F.Singurssonhh,SigfussonS.D.Manon. M.Steffnsson (2001) J International journal of pharmacy volume 212 p- 29-40 Cyclodextrinsolubilization benzodiazepine formulation of midazolam nasal spray.

[30] Machida Y. Nagai J (1974) J PharmaSci Tech 2346-2351. Compressed tablets containing hydroxypropylcelllose in addition to starch or lactose.

[31] MalletL. (1996) Caring for the elderly patient. J Am Pharma. Assoc:628.

[32] Merck Index (2001) An encyclopedia of chemical drugs and biologicals 13th edition Merck Research Laboratories, Division of Merck &Co Inc White house station N.J p-245.

[33] Martin Del Valle, E.M (2004) J A review process biochemistry 39th p- 1033-1046

[34] Martindale & Westcott (1996) the extra pharmacopoeia 31st edition, Royal pharmaceutical society of Great Britain London p-435-436.

[35] Orjales-VeneroA,Beascoa-Alzola, E,Pablo,MLLD (1993) Process to prepare water dispersible tablets containing diclfenac E P 599-767

[36] P.V.SwamiS.H.Areefulla S. B.Shirs, S mithaGandra and B. Prashanth(2007)Indian jounnal of pharmaceutical sciences volume 69 p-834-836

[37] Orodispersible tablets of meloxicam usindisintegrant blends for improve efficacy

[38] Sastry, S, V (20030 An Over view of Fast Dispering Technologies AAPS annual meeting.

[39] SauravBhutani ,S.N.Hirmath *,P.V Swamy and S.A.Raju. Jf Scientific and Industrial research (2007) p-830 -834. Preparation& Evaluation of inclusion complexes of carvedilol.

[40] ScheirmeirS.Schmidt, P,C(2002) Fast dispersible ibuprofen tablets,Eropean journal of pharmaceutical sciences 15th p-295- 305

[41] Seager H(1998) J pharmapharmacol 50,p- 375-382 Drug Delivery products and the Zydis Fast Dissolving Dosage Form

[42] Shangraw, R,Mitrevej,A,Shah M,A (1990) A new era of tablet disitegrantsPharmatechnol 4:p-49-57.

[43] Shimpi ,S,Chauhan,B.Shimpi (2005) Acta pharmacological sessica volume 212 p- 29-40.”Cyclodextrins application in different routes of drug administration .

[44] Shirwaikar.A.A.(2004) Fast disintegration tablets of atenolol by dry granulation method Ind.J.Pharm.Sci 66 p-

422-426

[45] Shishu B.A Singh T (2005) J Indian j of Pharm Sci 69 p-80-84.Preparationof rapidly disintegrating in saliva containig bitter taste masked granules by compression method.

[46] Shukla Dali, SubhashisChakraborty,Sanjay Singh, Brameshwar Mishra(2009) J Sci.pharm. 2009. Mouth Dissolving Tablet II.An overview of evaluation techniques.

[47] Skinner, G.W.1999 J Drug Dev.IN Pharm, 25, P-1121-1128 The evaluation of fine particle hydroxypropylcellulose as a roller compaction binder in pharmaceutical applications.

[48] S.R Jones, D.J.W.Grant, J. Handgraft, and G.E Parr. Acta Pharm. Technol. 30, 213 (1984).

[49] Suarez, F.L., (1995) j N. Engl med 333,Acoparison of symptoms after the consumtion of milk or lactose-hydrolysed milk by people with self reported lactose intolerance. P-123-132.

[50] Szejtli,T, (1988) Cyclodextrin technology Kluwer Academic Publisher,Dordrecht.

[51] Tatsuya Ishikawa, Igarashi H, Suzuki.M, Uchiyama N. (2000) Br J, Pharmacol. 130, 132-138, Cisplastin induced early and delayed emesis in the pigeon,

[52] Thwaites,P.M. ,Maeshadi A.B, Moore W.D(1991) Drug Development Ind. Pharm. 17 p-503-517. An investigation of the effect of high speed mixing on the mechanical &physical properties of direct compression lactose.

[53] Toshifusa,S.H.U,HideshiS,Kenji, H.Kunio, I.T.O.(2002) Studies of Rapidly Disintegrating Tablets in the oral Cavity Using Coground Mixtures of Mannitol with Crospovidone Chem.Phar.Bull.50, 193-198.

[54] USP 27 National formulary 22 (2004), Rockville, Maryland, U.S Pharmacopoeial convention Inc, Rockville 2824-2933.

[55] USP Pharmacopoeia (2007) The united statePharmacopoeial convention Rockville Maryland

[56] US FDA 2007 Guidance for Industry,Orally Disintegrating Tablets,Center For Drug Evaluation and Research (CDER) Data Standard Manual.

[57] Van .K, Soik K.G (1992) US Patent 5 082, 667, Solid pharmaceutical dosage in tablet triturate form and method of producing the same.

[58] Watanabe .Y. (1995) J Biol.Pharm.Bull, New compressed tablet rapidly disintegrating in saliva in saliva in the mouth using crystalline cellulose and a disintegrant. Volume 18 p- 1308- 1310.

[59] W. Saenger. Angew. Chem. Int. Ed. Engl. 19,344 (1980)

[60] W. Saenger and S.R Jones, D.J.W.Grant, J.Hadgraft and G.E.Parr. (1965) J Acta Pharm. Technol. 30, 213 (1984) Enhancement of aquous solubility of itraconazole by complexation.

[61] Yarwood R.J, P Kearney. A.R Thompson 1998 J Man, Chem 51 p- 36-37 Fast Dissolving Dosage Form.