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DESIGN, DEVELOPMENT AND EVALUATION OF RAPIDLY DISSOLVING ORAL STRIPS OF HALOPERIDOL

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ABSTRACT

An attempt was made to design and evaluate Rapidly dissolving oral strips of Haloperidol which is an Anti-psychotic agent. Fast dissolving drug delivery system offers a solution for those patients facing problem in swallowing of solid dosage forms such as Pills, Tablets & Capsules etc. Pure Haloperidol Drug has less water solubility which is improved by using Beta-cyclodextrin complexation which was proved by phase solubility study. The Rapidly dissolving strips were prepared by solvent casting technique by using HPMC 5cps, Sodium CMC and PVA as the film forming polymers. The prepared strips were evaluated for the thickness, folding endurance study, surface pH, drug content and *in-vitro* disintegration and *in-vitro* dissolution studies. All the formulations fulfilled criteria for evaluating parameters. Drug content of formulations was found to be 89% to 98 %, disintegration time in the range of 17-29s, *in vitro* dissolution studies showed 76.86% to 98.53%. Hence it was concluded from the results obtained that, the Rapidly dissolving oral strips of Haloperidol can be successfully developed in order to enhance the dissolution rate, thereby better patient compliance and effective therapy.

Keywords: Fast dissolving oral strips; Rapidly dissolving oral strips; Haloperidol

Introduction[(1)]:

Among the delivery routes, the oral route is the most acceptable from patient compliance aspects. Many pharmaceutical firms have directed their research activity in reformulating existing drugs into new dosage forms. One such relatively new dosage form is the oral strip, a thin film that is prepared using hydrophilic polymers that rapidly dissolves on the tongue or buccal cavity. The surface of buccal cavity comprises of stratified squamous epithelium which is essentially separated from the underlying tissue of the lamina propria and submucosa by an undulating basement membrane. It is interesting to note that the permeability of the buccal mucosa is greater than that of the skin, but less than that of the intestine[(2,3,4)]. Hence the buccal delivery serves as an excellent platform for absorption of molecules that have poor dermal penetration. However, the primary barrier to permeability in the oral mucosa is the result of intercellular material derived from the so-called 'membrane coating granules' present at the uppermost 200 micron layer.[(5,6)]

To make the ease of administration and swallowing, pharmaceutical research has led to the develop the Oral Disintegrating Tablets (ODTs). ODTs have been defined as "A solid dosage form containing medicinal substances which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue". United States Food and Drug Administration further defines ODTs as solid oral preparations that disintegrate rapidly in the oral cavity, with an in-vitro disintegration time of approximately 30s or less, when based on the United States Pharmacopeia (USP) disintegration test method or alternative. Also, Research and development in the oral drug delivery segment has led to transition of dosage forms from simple conventional tablets/capsules/Pills to modified release tablets/capsules/Pills to oral disintegrating tablet (ODT) to wafer to the recent development of oral strip (OS). Basically the OS can be considered as an ultra-thin strip of postage stamp size with an active agent or active pharmaceutical ingredient and other excipient. The advantages of convenience of dosing and portability of OS have led to wider acceptability of this dosage form by pediatric as well as geriatric population equally.

- **Materials and Method :-**

1) Material :-

Haloperidol obtained from Life sciences Ltd. Mumbai. Beta-cyclodextrin obtained from Yarrow Chem Products, Mumbai, India.

Hydroxy Propyl Methyl Cellulose (HPMC), Poly vinyl Alcohol (PVA) & Sodium CMC Were obtained from Loba chemicals Ltd.

- **Preparation of Phosphate buffer pH 6.8 :**

It was prepared by placing 250 ml of potassium di-hydrogen orthophosphate solution and 112 ml of 0.2 M NaOH solution and volume was make up to 1000 ml with distilled water .the pH of buffer solution was found to be 6.8

➢ **Method Of Preparation Of Rapidly Dissolving Strips :-**

One or more of the following process can be used combinly to manufacture the mouth dissolving films.

- Solvent casting
- Semisolid casting
- Hot melt extrusion
- Solid dispersion extrusion
- Rolling

➢ **Solvent casting method**[21]

In solvent casting method excipient are dissolved in water, then water soluble polymers and in last drug is added and stirred to form homogeneous solution. Finally solution is casted in to the Petri plate and dried.

➢ **Formulation of rapidly dissolving strips of Haloperidol :**

1) **Solvent casting technique**:

The strips were prepared by using polymers HPMC 5cps,Sodium CMC,PVA and Glycerine was used as a plasticizer. The calculated amount of polymer was dispersed in three forth volume of Haloperidol with continuous stirring using magnetic stirrer and the final volume was adjusted with distilled water. Calculated amount of Haloperidol was incorporated in the polymeric solution after levigation with the required volume of Glycerine.The solution was casted and kept in hot air oven at 37°c strips of various formulations are mentioned in table. By carrying out the trial and error method different concentrations of strips forming polymers were used like HPMC,Sodium CMC & PVA. Concentrations of strips were prepared by dissolving different quantities of film forming polymers in 10 ml of water.

➢ **Analytical Methods :-**

1) Identification of Drug :

➢ **Description:**

The sample of Haloperidol was analysed for physical appearance, powder nature and from COA (Certificate of analysis) of the drug.

➢ **Melting point**[51]

Melting point of the pure drug was determined by using melting point apparatus. The thermometer used was previously calibrated. The method consists of placing the powdered compound in a calibrated tube

and heated in Thiele apparatus. The temperature at which sample start melting is considered as lower limit and at which completely melt is considered as upper limit of melting range. The obtained result compared with the values in literatures.

2) Calibration curve for the estimation of Haloperidol[59] :-

50 mg of Haloperidol was weighed and dissolved in 50 ml of phosphate buffer (pH 6.8) in a volumetric flask (stock solution l) from stock solution I, 2 ml was taken and the made up to100 ml with phosphate buffer (pH 6.8) (stock solution II). From Stock solution II, serial dilutions were made to make series of 2, 4, 6, 8, 10, µg/ml solution and UV Absorbance was noted at 242.2 nm, using phosphate buffer (pH 6.8) as blank.

- **Compatibility of drug with excipients[60,61] -**

1) FTIR Spectroscopy:

IR spectra of pure drug and mixture of drug and excipients were taken to check the compatibility of drug with excipients. IR Spectra were taken from 600-4000 $cm^{-1.}$

2) Differential Scanning Calorimetry :

From thermal analysis techniques, particularly Differential Scanning Calorimetry (DSC), when critically examined has been found useful in rapid screening for possible drug-additive and drug-drug interactions. Thermal analysis can be used to investigate and predict any physico-chemical interactions between components in a formulation and can therefore be applied to the selection of suitable chemically compatible excipients. An interaction on DSC will show as changes in melting point, peak shape and area and/or the appearance of a transition.

3) Phase Solubility Studies[62]

Phase solubility studies were carried out according to the method reported by Higuchi and Connors. An excess of Haloperidol was added to 15 ml portions of 6.8 pH buffer medium each containing variable amount of β -CD in 0, 2, 4, 6, 8,10 x 10^{-3} moles/liter. All the above solutions with variable amount of β -CD were shaken for 72 hours. After shaking, the solutions were filtered and their absorbance was noted at 242.2 nm. The solubility of the Haloperidol in every β –CD solution was calculated and phase solubility diagram was drawn between the solubility of Haloperidol and different concentrations of β –CD as shown in fig.7

- **Formulation of rapidly dissolving strips of Haloperidol :**

Solvent casting technique:

The strips were prepared by using polymers HPMC 5cps,Sodium CMC,PVA and Glycerine was used as a plasticizer (in table no 4). The calculated amount of polymer was dispersed in three forth volume of Haloperidol

with continuous stirring using magnetic stirrer and the final volume was adjusted with distilled water. Calculated amount of Haloperidol was incorporated in the polymeric solution after levigation with the required volume of Glycerine.The solution was casted and kept in hot air oven at 37°c strips of various formulations are mentioned in table. By carrying out the trial and error method different concentrations of strips forming polymers were used like HPMC,Sodium CMC & PVA. Concentrations of strips were prepared by dissolving different quantities of film forming polymers in 10 ml of water.

- **Evaluation Of Strips**

Prepared fast dissolving strips were evaluated for the following parameters.

a) Physical appearance and surface texture
b) Weight uniformity of strips
c) Thickness of strips
d) Folding endurance of strips
e) Surface pH
f) *In vitro* disintegration time
g) Drug content uniformity
h) *In vitro* drug release

a) Physical appearance and surface texture

This parameter was checked simply with visual inspection of films and evaluation of texture by feel or touch.

b) Weight uniformity of strips[64]

Three strips in a formulation batch were weighed individually using digital balance and average weights were calculated.

c) Thickness of strips[65]

Thickness of the films was measured using screw gauge with a least count of 0.01mm at different spots of the strips and average was taken.

d) Folding endurance of strips[66,67]

The folding endurance was determined by repeatedly folding one film at the same place till it broke. The number of times the film could be folded at the same place without breaking was consider as folding endurance value.

e) Surface pH[68]

The film to be tested was placed in a petridish and was moistened with 0.5 ml of distilled water and kept for 1hr. The pH was noted after bringing the electrode of the pH meter in contact with the surface of the formulation and kept for 1 min to allow equilibrium condition.

***f) In-vitro* disintegration time**

Disintegration test was performed by placing the strip in the glass petri dish containing 20 ml of water. It was stirred at every 10 second time interval. The time required for the strip to disintegrate was recorded.

g) Drug content uniformity[69]

Weight equivalent to 5 mg was taken and transferred to 100 ml of 6.8 pH phosphate buffer in volumetric flask. The volume was made with 100ml pH phosphate buffer, the solution was filtered through Whatman filter paper and absorbance was measured at 242.2 nm by using UV Spectrophotometer.

***h) In-vitro* drug release study[41]**

In-vitro dissolution was performed by using the following conditions:

- USP-II apparatus
- Rotation speed- 50 rpm
- Temperature- 37 ± 0.5^0C
- Media – pH 6.8 phosphate buffer
- Media volume- 900 ml
- Sample withdrawal- 5ml
- The sample was filtered and absorbance was measured at 242.2 nm.
- An equivalent volume of phosphate buffer was replaced with fresh buffer into the dissolution bath, to maintain the constant dissolution medium.

4.6.1 Stability studies:

Introduction:

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature,humidity and light, enabling recommended storage conditions, re-test periods and shelf-life.

. Stability studies were carried out at 40^0C/75% RH for the selected formulation for the period of 30 days. Samples were taken after 30 days & strips were evaluated for surface PH, drug content study, *In-vitro* disintegration time, *In-vitro* drug release study**.**

Results and Discussion :-

1) Calibration Curve of Haloperidol :

The UV Spectrum of drug in the range of 200-400 nm on UV Spectrophotometer revealed that ƛ max of Haloperidol was at 245 nm. From the plot of absorbance vs Concentration of pure Haloperidol, it was observed that the drug obeys beer's-lambert's law in the concentration

Sr. No.	Vol. Made up to (ml)	Conc. (µg/ml)	Absorbance
1	10	0	0
2	10	2	0.097
3	10	4	0.168
4	10	6	0.250
5	10	8	0.360
6	10	10	0.434

Table No. 1 :- Calibration Curve of Haloperidol

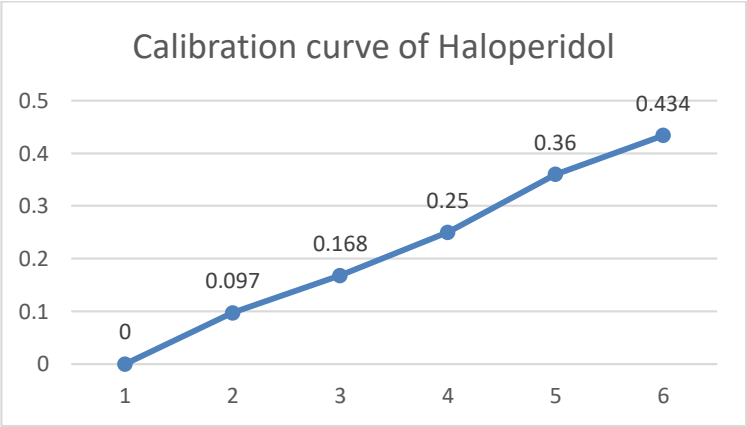

Figure No. 1 - Calibration curve of Haloperidol

2) *Differential Scanning Calorimeter* Study :-

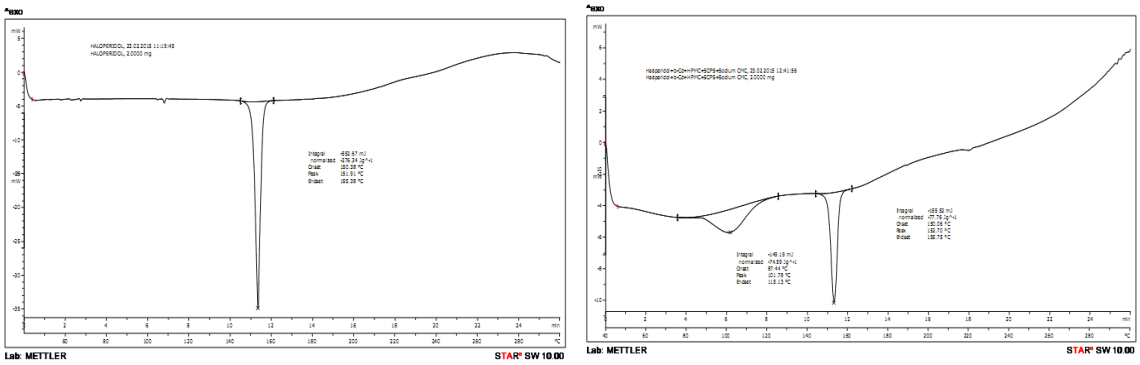

Figure No. 2 - Differential Scanning Calorimetry Curves

3) Phase Solubility Study of Haloperidol :-

Phase solubility studies were carried out according to the method reported by Higuchi and Connors. An excess of Haloperidol (200 mg) was added in 15 ml of portions of distilled water, each containing variable amount of β-CD in 0,2,4,6,8,10 X 10^{-3} moles/litre. All the above solutions with variable amount of β-CD were shaken for 72 hr. After shaking, the solutions were filtered and their absorbance were noted at 245 nm. The solubility of the Haloperidol in every β-CD solution was calculated and phase solubility diagram was drawn between the solubility of Haloperidol and different concentrations of β-CD.

Sr. No.	Concentration of Beta-cyclodextrin (mM)	Concentration of Haloperidol (mM)
1	0	0.56
2	2	1.00
3	4	1.50
4	6	1.97
5	8	2.45
6	10	2.95

Table No. 2 - Phase Solubility Study

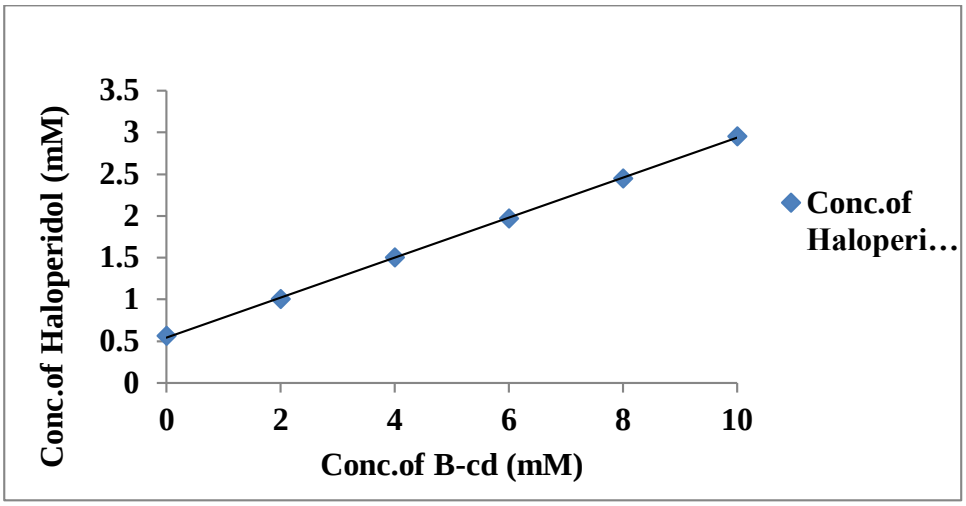

Figure No. 3 - Phase Solubility Study Curve

4) Folding Endurance Test :-

Formulation Code	Folding Endurance (times to break)
F1	200.66±30.53
F2	241.33±09.01
F3	233.66±27.53
F4	247.00±17.77
F5	282.33±09.45
F6	227.66±12.50
F7	235.00 ±12.50
F8	234.00±12.50
F9	250.34±10.25
F10	270.50 ±11.45
F11	246.24±10.32

Table No. 3 . Folding endurance of fast dissolving Oral Strips of Haloperidol

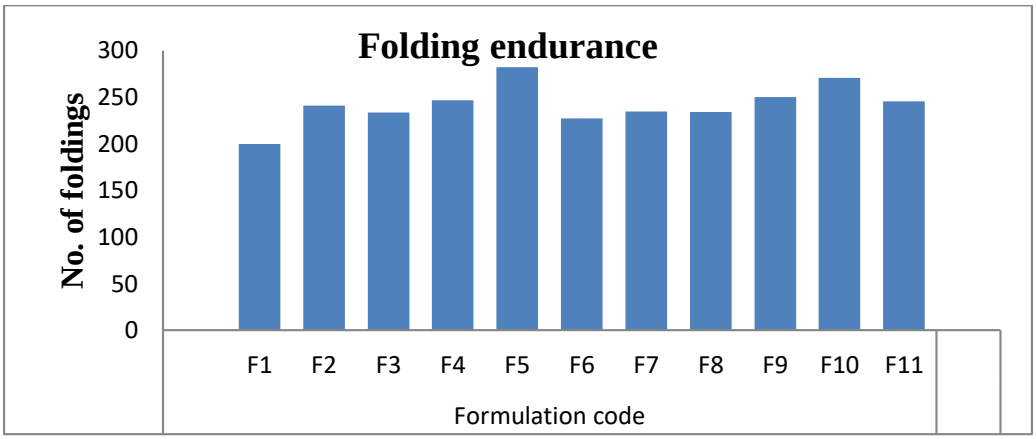

Figure No. 4 - Folding Endurance Curve

5) Surface pH, Disintegration Time & Percent Drug Content :-

Formulation Code	Surface pH	Disintegration time (sec)	Drug Content %
F1	7.03	28.64	95.73±0.745
F2	7.10	25.33	89.12±0.432
F3	7.06	19.66	98.45±0.206
F4	7.01	22.64	96.83±0.257
F5	6.87	19.00	96.00±0.296
F6	6.92	17.66	98.30±0.605
F7	7.04	18.27	94.56±0.297
F8	6.60	20.22	97.63±0.745
F9	7.00	24.23	92.32±0.296
F10	6.90	21.21	95.21±0.432
F11	6.80	19.90	94.24±0.257

Table No. 4 - Surface pH, Disintegration time and Drug Content of Rapidly dissolving Oral Strips of Haloperidol.

6) Dissolution study :-

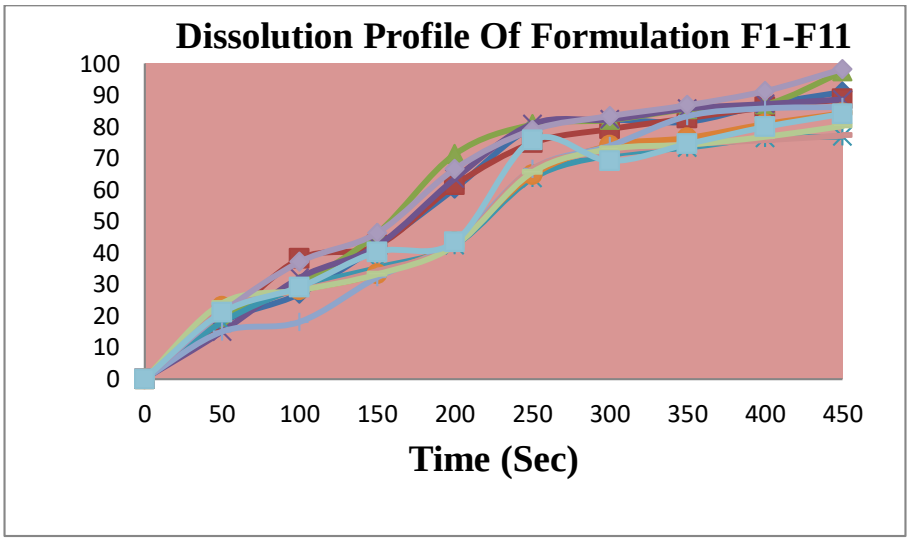

Figure No. 5 - Dissolution profile of Rapidly Dissolving oral strips of Haloperidol

7) Percent Drug Release :-

Time	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
0	0	0	0	0	0	0	0	0	0	0	0
50	18.00	18.00	19.00	15.00	18.00	23.00	15.00	23.00	24.00	21.00	21.00
100	27.01	38.1	30.01	32.08	29.01	28.12	18.08	28.12	28.13	37.11	29.11
150	42.15	42.31	46.17	42.25	35.26	33.27	32.18	34.27	33.18	46.31	40.27
200	60.38	61.54	71.32	63.48	42.45	43.45	43.34	42.45	42.36	66.56	43.47
250	79.71	74.87	80.71	80.83	63.68	64.68	66.57	66.68	65.59	78.92	75.70
300	82.14	79.28	82.15	82.27	71.03	74.04	73.93	72.04	72.95	83.35	69.10
350	81.59	82.71	85.6	85.72	73.41	76.44	83.33	74.43	74.34	86.80	74.4
400	87.04	86.16	87.06	87.18	76.45	80.85	85.78	75.80	76.83	91.26	79.87
450	91.50	88.69	97.52	88.64	76.86	84.28	86.24	77.21	80.24	98.27	84.03

Table No. 5 - Drug Release Percentage Values

8) Scanning Electron Microscope (SEM) Photograph :-

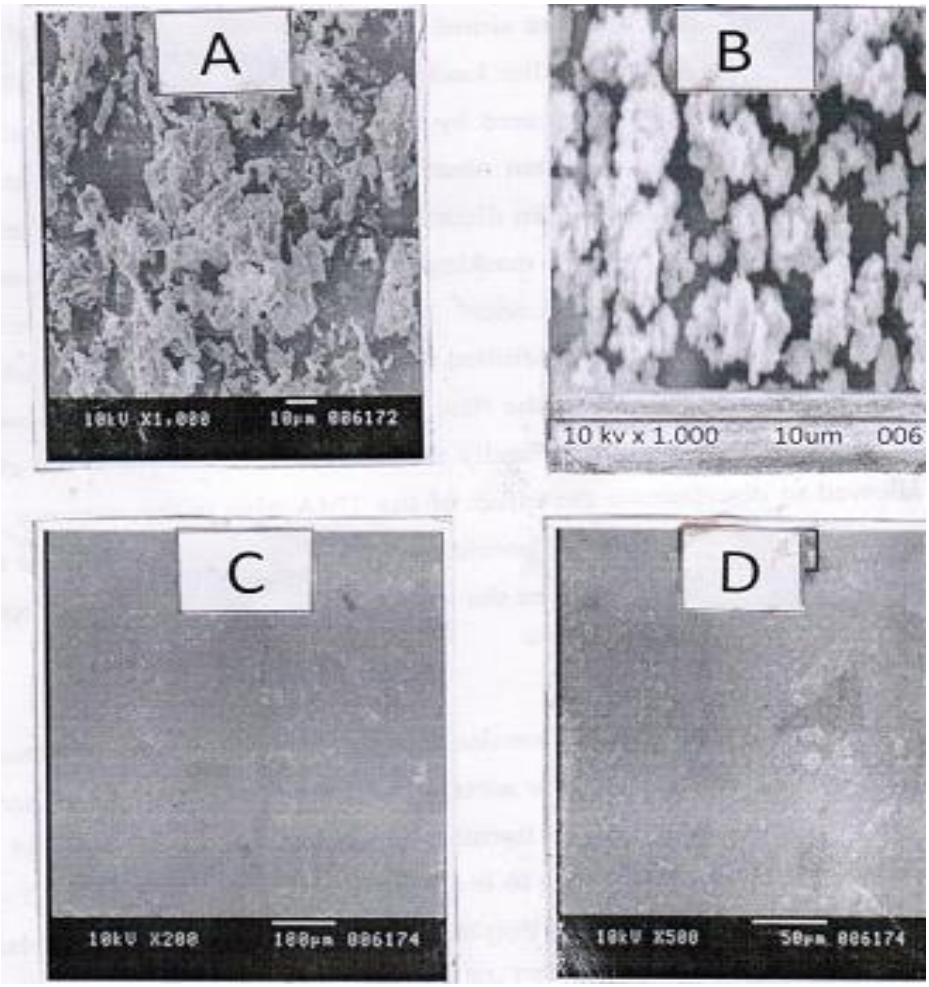

Figure No. 6. SEM photograph of rapidly dissolving oral strip formulation

Figure A = Haloperidol,

Figure B = Beta cyclodextrin,

Figure C = Optimized formulation F3,

Figure D = Optimized formulation F10.

9) Stability Test of F4 & F10 formulation :-

The selected formulations were based on disintegration time & % drug release evaluated for stability studies which were stored at 40°C at 75% RH tested for 30 days and were analysed for their physical parameters, disintegration time, % drug content & % drug release at the end and the results were shown in Table. No. 6

Formln / Time (Days)	Physical appearance		Disintegration time (Sec)		% drug content		% drug release	
	F4	F10	F4	F10	F4	F10	F4	F10
1st Day	++	+++	21.21	21.21	95.08	96.08	88.64	98.27
30th Day	++	+++	21.16	21.18	94.97	95.92	88.17	97.95

++ indicates good, +++ indicates excellent

Table No. 6 - Stability data of F4 & F10 formulation

Conclusion :-

Among the oral drug delivery systems, The oral strip formulations gives a solution to the patients who facing swallowing difficulties for administration of pills, tablets & such type of formulations.

Hence, On the basis of study carried out & their results obtained it can be concluded that, The fast dissolving strips of haloperidol with swellable polymer like HPMC, Sod. CMC & PVA could developed successfully by solvent casting technique with respect to enhance the dissolution rate. There by a better patient compliance can be achieved for better hypertension therapy.

References -

1. Deepak H, Aggarwal G, Hari Kumar S; Fast dissolving films: an innovative drug delivery World J Pharm Res; 2; (5) 1423-39.
2. Y. Rojanasakul, L.-Y. Wang, M. Bhat, D.D. Glover, C.J. Malanga, J.K.H. Ma, The transport barrier of epithelia: a comparative study on membrane permeability and charge selectivity in the rabbit, Pharm. Res. 9 (1992) 1029–1034.
3. A.V. Gore, A.C. Liang, Y.W. Chien, Comparative biomembrane permeation of tacrine using yucatan minipigs and domestic pigs as the animal model, J Pharm Sci 87 (1998) 441–447.
4. A.H. Shojaei, Buccalmucosa as a route for systemic drug delivery: a review, J Pharm Pharm Sci 1 (1998) 15–30.
5. R.B.Gandhi,J.R.Robinson,Oral cavity as a site for bioadhesive drug delivery, Adv Drug Del Rev 13 (1994) 43–74.

6. P.W. Wertz, C.A. Squier, Cellular and molecular basis of barrier function in oral epithelium, Crit Rev Ther Drug Carr Sys 8 (1991) 237–269.
7. S. Ganga, mucosal drug delivery – A review,Vol. 5 issue 6, 2007.
8. Mucoadhesive drug delivery systems; A Review.
9. Asane G.S., Mucoadhesive Gastro Intestinal Drug Delivery System: An Overview,Pharmainfonet.com. 2007, 5(6).
10. Bhalodia R. et al., Buccoadhesive drug delivery systems: a review, Int J Pharm. Bio Sci. 2010, 6 (2).
11. Dodou D. et al., Mucoadhesives in the gastrointestinal tract: revisiting the literature for novel applications. Eur J Pharm Biopharm.2005, 60, 1-16.
12. Lee J.W. et al., Bioadhesive-based dosage forms: the next generation. J Pharm Sci 2000, 89, 850-66.
13. Chowdary K.P.R., Srinivas L.,Mucoadhesive drug delivery systems: A review of current status, *Indian Drugs*, 2000, 37(9), 400-406.
14. Gandhi R.B., Robinson J.R., Bioadhesion in drug delivery. *Indian. J Pharm Sci*. 1988, 50(3), 145-152.
15. Muthukumaran et.al,Mucoadhesive buccal drug delivery system-A promising alternative for oral efficient poor drugs,American journal of pharmatech research 2013.
16. N.A.Peppas,P.A.Buri,Surface, interfacial and molecular aspects of polymer bioadhesion on soft tissues, J. Control. Release 2 (1985) 257–275.
17. Schenkels, T.L. Gururaja, M.J. Levine, in: M.J. Rathbone (Ed.), Oral Mucosal Drug Delivery, Marcel Dekker, New York, 1996, pp. 191–220
18. .D. Harris, J.R. Robinson, Drug delivery via the mucous membranes of the oral cavity, J Pharm Sci 81 (1992) 1–10.
19. Technology catalysts International Corporation, http://www.technology-catalysts.com.(http://www.technologycatalysts.com/pdf/ODT_PressRelease-0106.pdf.
20. H. Zhang, J. Zhang, J.B. Streisand, Oral mucosal drug delivery: clinical pharmacokinetics and therapeutic applications, Clin. Pharmacokinet. 41 (9) (2002) 661–680.[28] http://www.gas-x.com/
21. Arya A and Chandra A: Fast Dissolving Oral Films: An Innovative Drug Delivery sysem & dosage form.International Journal of Chem Tech Research 2010;2,576-583.
22. Alpesh R. Patel, Dharmendra S. Prajapati, Jignyasha A. Raval: Fast Dissolving Films (FDFS) as a Newer Venture in Fast. Int.J.Drug Dev. & Res. 2010; 2, 2: 0975-9344.
23. Coppens, K.A., M.J. Hall, S.A. Mitchell and M.D. Read, 2005. Hypromellose, Ethyl cellulose and Polyethylene oxide used in hot melt extrusion. Pharmaceutical Technol., pp: 1-6.
24. Mundhe B.Kadam V,Jadhav S.:A Short Review On Fsat Dissolving Strip Oral.World Journal Of Pharmacy & Pharmaceutical Sciences 2014;3,3:463-475.
25. Essential of medical Pharmacology, 6th edition, by KD Tripathi, Page no. 502-511.
26. Borison,R.L.(1997)Recent advances in the pharmacotherapy of schizophrenia. *Harv. Rev. Psychiatry* 4(5), 255-71.
27. Baldessarini, R. J. and Frankenburg, F. R. (1991) Clozapine. A novel antipsychotic agent. *N. Engl. J. Med.* 324(11), 746-54.

28. Dennis R.Grayson,Alessandro Guidotti & Errinia Costa.An Epigenetic Hypothesis for Schizophrenia Pathophysiology.2007.Jan 8;18(1):57-60.
29. Essential of medical Pharmacology,6th edition ,by KD Tripathi ,Page no.423-43.
30. Cilurzo F, Cupone IE,Minghetti P,Buratti S, Chiara GM, Gennari, Montanari L.Diclofenac fast-dissolving film: suppression of bitterness by a taste-sensing system. Drug dev Ind Pharm 2011; 37: 252–59.
31. Komaragiri SD, Shaik F, Yerram C, Vardhan VR, Amaravathi V, Uttaradi A.Formulation and characterization of atenolol fast Dissolving films. Indian J Pharm Sci Res. 2012; 2 (2):58-62.
32. Amin A, Mishra R, Formulation and characterization of rapidly dissolving films of Cetrizine Hydrochloride using Pullalan as a film forming agent. Indian J Pharm Edu Res 2011; 45,1.
33. Parejiya PB, Patel RC, Mehta DM, Shelat PK, Barot BS, Quick dissolving films of Nebivolol hydrochloride: formulation and optimization by a simplex lattice design. J Pharm Invest 2013.
34. Londhe VY, Umalikar KB. Formulation development and Eval fast dissol film of Telmisartan Indian J Pharm Sci 2012.
35. Kunte S, Tandale P. Fast dissolving film strips: A novel approach for the delivery of Verapamil. J Pharm Bioallied Sci 2010; 2.
36. Joshi P, Patel H, Patel V, Panchal R. Formulation development and evaluation of mouth dissolving film of Domperidone. J Pharm Bioallied Sci 2012; 4: 108-9.
37. Panchal MS, Patel H, Bagada A,.Vadalia KR; Formulation and Evaluation of mouth dissolving film of Ropinirole HCl by using Pullulan Polymers; Int J of Pharm Res Allied Sci 2012; 1,60-72.
38. Reddy R,Muzib Y.,Chowdhary K.,Development & in-vivo characterisation of novel trans buccal formulation of Amiloride hydrochloride.Journal of Pharmacy Research 6(2013),647-652.
39. Dinge A,Nagarsenker M. Formulation and evaluation of fast dissolveing films for delivery of triclosan to the oral cavity.AAPS Pharm Sci Tech.2008;9(2):349-56.
40. 40.Nagar M,Nagar M & Chopra V,Formulation& evaluation of mouth dissolving film of Antipsychotic drug Aripiprazole.DerPharmacia Lettre,2012,4(4):1221-1227.
41. Bansal S,Bansal M,,Garg G.Formulation and evaluation of fast dissolving film of Antihypertensive drugs.An International Journal Of Pharmaceutical,Chemical & Biological Sciences 2013,3(4),1097-1108.
42. Kumar S ,Nagabhushanam M,Rao R.S.,Bhikshapathi D,Preparation & in vivo evaluation of oral dissolving films containing Sumatriptan succinate.Der Pharmacia Letter 2013,5(3):27-38.
43. Liew K,Tan Y & Peh K.Characterisation of oral dissolving film containing Donepezil for Alzheimer Disease.AAPS Pharm Sci Tech:2012 Mar;13(1):134-142.
44. Kulkarni P.Dixit M,Gunashekara K,Shahanwaz A, Singh M & Kulkarni A.Formulation & evaluation of fast dissolving film containing Rofecoxib.International Research Journal Pharmacy 2011,2(3):273-278.
45. Shelke PV, Dumbare AS, Gadhave MV, Jadhav SL, Sonawane AA, Gaikwad DD, Formulation and Evaluation of rapidly disintegrating film of amlodipine besylate, J Drug del Th 2012; 2.

46. Desu P, Shahu M; Formulation and evaluation of fast dissolving films of Zolmitriptan; Res Article Int Res J Pharm 2012; 3.
47. Swamy NG, Shiv kumar S; Formulation and Evaluation of fast dissolving oral films Palonosetron hydrochloride; Int J Pharm Chem Res; Res Article 2014, 3 (1).
48. Prameela Rani, Siva Teja. P, Archana. N, Bala Sekaran. C. Phase solubility studies on oral antidiabetic drugs with β-cyclodextrin and HP–β-cyclodextrin Int J Pharm Tec Rec. 2009; 1: 1632-37.
49. Fernandes CM, Vieira TM, Veiga FJB. Physicochemical characterization and *in vitro* dissolution behavior of nicardipine–cyclodextrins inclusion compounds. Eur J Pharm Sci. 2002; 15: 79–88.
50. Nie Shufang, Zhang Shu, Pan Weisan, and Liu Yanli. *In vitro* and *in vivo* studies on the complexes of glipizide with water-soluble β-cyclodextrin–epichlorohydrin polymers. Drug Dev Ind Pharm. 2011; 37: 606–12.
51. United States of Pharmacopoeia, NF. Asian edition 2004, the official compendia of standards; 1229-300.
52. Rowe RC, Sheskey PJ, Quiun ME.Handbook of Pharmaceuticall excipients, 6th edition Choicago 2009.326-29.
53. Rowe RC, Sheskey PJ, Quiun ME.Handbook of Pharmaceuticall excipients, 6th edition Choicago 2009.564-65.
54. Rowe RC, Sheskey PJ, Quiun ME.Handbook of Pharmaceuticall excipients, 6th edition Choicago 2009.185-186.
55. Rowe RC, Sheskey PJ, Quiun ME.Handbook of Pharmaceuticall excipients, 6th edition Choicago 2009.206-207.
56. Rowe RC, Sheskey PJ, Quiun ME.Handbook of Pharmaceuticall excipients, 6th edition Choicago 2009.433-434.
57. Rowe RC, Sheskey PJ, Quiun ME.Handbook of Pharmaceuticall excipients, 6th edition Choicago 2009.557-561.
58. Indian Pharmaopoeia.Govt.of India,ministry of health & family welfare,Delhi : controller of India New Dehli,India 2007.Appendix 13.1 A-145.
59. Yasir M.,Sara U.V.S.Development & Validation of UV spectrophotometric method for the Estimation of Haloperidol British Journal of P'ceutical Reaserch 2014.4(11) : 1407-1415.
60. Indian pharmacopoeia, Govt. of India, Ministry of health and family welfare, Delhi: controller of India: New Delhi, India, 2007:1; appendix 4.4, 550, 135-7, 179-83.
61. Wells J. Pharmaceutical Preformulation: The physicochemical properties of drug substances, In: Aulton M. Pharmaceutics: The science of dosage form design, 2 nd ed, Churchill Livingstone, Longman group, Edinburgh; 2002: 114-38.
62. Indian pharmacopoeia Gov.of India, Ministry of health and welfare Delhi: controller of India. 2007: A-144-47.
63. Aboul-Enein H.Y et al. Improvement of water solubility and *in-vitro* dissolution rate of gliclazide by complexation with β-cycldextrin. Pharm acta Helvetiae. 2000; 74: 365-70.

64. Jain S.k, Agrawal G.P, Jain N.K, Evaluation of porous carrier- bared floating orlistat Microsphere for gastric delivery, AAPS Pharm Sci Tech, 2006; 7(4) :90.
65. Sandeep D Jadhav, Rahul N kalambe, Chethan M Jadhav, Bharat W Tekade, Vijay R Patel. Formulation and evaluation of Fast Dissolving Films of Levocetirizine dihydrochloride. International journal of Pharmaceutical sciences, 2012; 1(2): 99-104.
66. Shimoda. H, Taniguchi. K, Preparation of fast dissolving oral thin film containing Dexamethasone: A possible application to antiemesis during cancer chemotherapy. Eur J Pharm. Biopharm, 2009; 73: 361-365.
67. Kunte S.,Tandale P. Fast dissolving oral strips for the delivery of Verapamil. J Pharm and Bio alli Sci, 2010; 2(4):325-328.
68. Sumitha CH, Karuna. SN, Divya, B, Madhavi. K, Vimal Kumar Varma. M, Charbe NN.Taste masking of Ondansetron HCL by polymer carrier system and formulation of rapid-disintegrating films. Int J Chem res, 2009; 1(2):24-27.
69. Koland. M, Sundeep. VP, Charyulu. NR. Fast Dissolving Sublingual Films of Ondansetron hydrochloride: Effect of additives on In vitro drug release and mucosal permeation. JYoung pharmacist, 2010; 2(3): 216-22.