Vol 5|Issue 2| 2015 |143-151.

International Journal
of
Pharmacy Review & Research
www.ijprr.com

e-ISSN: 2248 – 9207
Print ISSN: 2248 – 9193

FORMULATION AND EVALUATION OF ZOLPIDEM TARTRATE SUBLINGUAL TABLETS

Meesa.Rajendar*[1], Beedha Saraswathi*[1]

Pharmaceutics, Assistant professors in St.John College of pharmacy,

ABSTRACT

In the present study 3.5 mg strength will be going to be prepared and also evaluated for all the physical parameters evaluation and in-vitro drug dissolution studies. The first strategy was developed based on innovator composition to study and evaluate all the parameters. The second strategy was developed as generic version to the innovator by using microcrystalline cellulose and Mannitol of different grades and evaluated for all physical parameters and drug release. First the formulation was designed without incorporating buffering agents and after achieving the satisfactory formulation, buffer system was finally incorporated and new formulation was designed, however this formulation which was made by incorporating the single buffering agent failed to achieve the specifications required for the generic version of INTERMEZZO®. The third strategy was developed as generic version to the innovator by using F-Melt and Mannitol combination to improve the flow properties and the achieving good content uniformity with faster disintegration. The formulation that was developed by direct compression failed to achieve content uniformity and faster disintegration and therefore, wet granulation was preferred. The formulation F9 was designed by wet granulation and evaluated for all physical parameters and also drug release. The formulation F9 has good flow properties, content uniformity and drug release but slightly higher disintegration time was observed. Now this formulation was selected for optimization to achieve faster disintegration time and also single buffer system was incorporated. The final optimized formula F10 was designed so that faster disintegration time was achieved with improved content uniformity, flow properties and drug release. This formulation is competed for the innovator INTERMEZZO® sublingual tablets.

Key words: Sublingual tablets, Intermezzo, Zolpidem tartrate, Prefromulation studies, Post formulations studies, Sedative-hypnotic drug.

INTRODUCTION

Sublingual Drug Delivery System is one of the delivery system that is designed to overcome the challenges that we encounter in oral drug delivery and offer advantages that may not be obtained by any other delivery system. The active ingredient must be absorbed into the systemic circulation to exert its pharmacological effect, and it can be administered by three major route [1]. The movement of drug from the site of administration to the systemic circulation, the absorption may be from [2],

- GIT, rectum,
- Mucosal lining of buccal cavity, sublingual glands, vagina, nasal cavity,
- Pulmonary,
- Intraocular,
- Intramuscular and subcutaneous,
- Topical.

Hence Sublingual drug delivery system is enteral route of administration, but as far as absorption is concerned, it is oral transmucosal type of drug absorption. Sublingual drug delivery systems have been introduced to overcome the drawback of low bioavailability problems associated with conventional oral dosage forms. Therapeutically active molecules for the treatment and prevention of new and existing diseases are currently being developed [3-4].

Although pharmacological activity is the primary requirement for a molecule to be used as a therapeutic agent, it is equally important that the molecule reaches its site of action, and hence drug delivery technologies have assumed importance [5]. Nevertheless, many existing and new molecules provide challenges of poor pharmacokinetics leading to low bioavailability [6]. Drug

***Corresponding Author Meesa Rajendar** E mail: meesarajendar26@gmail.com

delivery systems such as sublingual dosage forms are used to overcome these challenges. The cost of these drug delivery technologies is considerably low and substantially less than the cost of developing a new molecule. Hence, a continued interest exists in developing novel drug delivery systems for the delivery of active agents [7].

Sublingual formulations are to be placed under the tongue and produce immediate systemic effect by enabling the drug absorbed directly through mucosal lining of the mouth beneath the tongue. The drug absorbed from stomach goes to mesenteric circulation which connects to stomach via portal vein. Thus, absorption through oral cavity avoids first-pass metabolism. Also rapid onset of action can be achieved with the use of sublingual tablets [8].

These are designed to dissolve in small quantity of saliva. After the dosage form is placed in the mouth below the tongue, the patient should avoid eating, drinking, smoking and possibly talking in order to keep the formulation in place. Swallowing of saliva should also be avoided since the saliva may contain dissolved drug. Bland excipients are used to avoid salivary stimulation [8-9].

Advantages

1. The liver is by-passed thus there is no loss of drug by first pass effect for sublingual administration, So Bioavailability is higher [10-13].
2. Because of good blood supply to the area absorption is usually quite rapid
3. pH in mouth relatively neutral so a drug may be more stable.
4. A relatively rapid onset of action can be achieved compared to the oral route, For Example, Glyceryl Trinitrate, a potent coronary vasodilator which is used for the rapid symptomatic relief of angina. It has been found impressively effective when administered sublingually; pharmacologically active within 1 - 2 minutes.
5. Liver is bypassed and also drug is protected from degradation due to pH and digestive enzymes of the middle gastrointestinal tract [13, 14].
6. Improved patient compliance due to theelimination of associated pain with injections; administration of drugs in unconscious or incapacitated patients.
7. Low dosage gives high efficacy as hepatic first pass m etabolism is avoided and also reduces the risk of side effects. It has been shown that the sublingual administration of 17-β Oestradiol requires only 1/4 of the oral dose.
8. The large contact surface of the oral cavity contributes to rapid and extensive drug absorption.
9. Due to rapidity in action thesesublingual dosage forms are widely used in emergency conditions e.g, asthma.
10. Rapid absorption and higher blood levels due tohigh vascularization of the region and therefore particularly useful for administration of antianginal drugs.
11. They also present the advantage of providing fast disi ntegration in the oral cavity, without the need for water or chewing. For example, some of the drugs like Desoxycortisone acetate, Morphine, Captopril, Nifedipine and 17, β - Oestradiol give impressive absorption when given sublingually [15-20].

Disadvantages

1. Holding the dose in the mouth is inconvenient. If any portion is swallowed that portion must be treated as an oral dose and subject to first pass metabolism.
2. Only small doses can be accommodated easily.
3. Since sublingual administration of drugs interferes with eating, drinking and talking this route is generally considered unsuitable for prolonged administration.
4. This site is not well suited to sustained delivery systems.
5. Sublingual medication cannot be used when a patient is un-cooperative or unconscious.
6. The patient should not smoke while taking sublingual medication, because smoking causes vasoconstriction of the blood vessels. This will decrease the absorption of the medication [20-25].

MATERIALS AND METHODS

Materials

Pharmaburst®500 is procured from SPI Pharma, Ac-Di-Sol (Croscarmellose Sodium), Pearlitol (Mannitol) grades, Aerosil® 200 (Colloidal Silica), Syloid 244 FP (Colloidal Silica), Avicel (MCC) Grades , Prosolv® SMCC, PVP K30 are the gifted samples from Evonik Industries, F-Melt is procured from Fuji Chemicals, Crospovidone, L-HPC, Sucralose, Sodium Carbonate, Sodium Bicarbonate, Sodium Stearyl Fumarate are obtained from SD Fine Chemicals Limited.

Methods

STRATEGIES EMPLOYED

Strategy I

The first strategy will be going to be developed a formulation based on innovator composition. Pharmaburst is used as diluent in innovator composition. First a formulation will be prepared without using buffer systems and then effect of buffer system on pH was studied.

Strategy II

The second strategy will be going to be developed by using mannitol and microcrystalline cellulose as diluents. In this strategy first buffer system is not used and then buffer system will be incorporated and the difference of pH was observed.

Strategy III

The third strategy will be going to be developed by using F-Melt as diluent. In this strategy also first buffer system is not used and then buffer system will be incorporated and the difference of pH was observed.

FORMULATION DESIGN AND DEVELOPMENT

FORMULATION PROCEDURE FOR DIRECT COMPRESSION TABLETS (FORMULATIONS F1, F3, F5 & F8)

1. Dispensing: -Dispense accurately required quantities of Active ingredient and Inactive ingredients accordingly to the working formula.
2. Sifting:-Step 1: - Weighed quantities of API and diluents were sifted first through 40# mesh.
Step 2: - All the excipients were also passed through 40# mesh and mixed with step 1.
Step 4: - Yellow Iron oxide is passed through 100# mesh and mixed with above blend.
3. Mixing: -The above blend was uniformly mixed by shaking in a polybag for about 15 minutes.
4. Lubrication: -Finally Sodium Stearyl Fumarate is passed through 60# mesh & was added to above blend and mixed uniformly in a double cone blender for about 5 minutes.
5. Compression: -The lubricated blend was compressed using 6.5 mm round flat punch.

FORMULATION PROCEDURE FOR WET GRANULATION TABLETS (FORMULATIONS F2, F4, F6, F7, F9 & F10)
A. Intra Granular
1. Dispensing:-Dispense accurately required quantities of Active ingredient and Inactive ingredients accordingly to the working formula.
2. Sifting:-Weighed quantities of API, Disintegrating agent and required quantity of diluent was sifted first through 40# mesh and mixed uniformly by shaking for 15 minutes.
3. Granulation:-Prepare binder solution by dissolving PVP K-30 in water and added to the above blend and wet granules were prepared by mixing in a bowl for about 10 minutes.
4. Drying:-The granules were dried for about 1 hour at 55-60°c. Loss on Drying at 105°C was found to be 2.45%.
5. Sifting:-Sift the dried granules through 30# mesh.

B. Extra Granular
6. Sifting:-Step 1:- Sift remaining diluents through 40# mesh and mix with the dried granules.
Step 2:- Sift remaining excipients through 40# mesh and mix with above granules.
Step 3:- Finally sift colour Yellow Iron oxide through 100# and mix with above blend.
7. Lubrication:-Finally Sodium Stearyl Fumarate was sifted through 60# mesh & added to above blend and mixed uniformly in a double cone blender for about 10 minutes.
8. Compression:-The lubricated blend was compressed using 6.5 mm round flat punch.

RESULTS AND DISCUSSION

Drug Excipient Compatibility Studies
The preformulation studies were first conducted on physical mixtures and then analysed by HPLC whether any interaction lead to impurity formation.

The impurities that are explained in table 5 were formed are in negligible amount and all the excipients that are used are compatible with the drug. So, the Drug - Excipients compatibility studies of physical mixtures by HPLC has not showed any prominent interaction. However compatibility studies by FT-IR are also conducted.

Drug Excipient Compatibility Studies (By FT-IR)

In API Infra Red Spectrum the peaks and the functional groups are found to be Amides at C=O Stretching – 1680-1630 cm^{-}, Carboxylic Acid at C-O Stretching – 1320-1210 cm^{-1} O-H Bending – 1440-1400 cm^{-1}, Imines at R_2C=N-R – Stretching – 1690-1640 cm^{-1}.

In Placebo Infra Red Spectrum the peaks and the functional groups are found to be at Amines at N-H stretch - 3500-3300 cm^{-1}, Alcohols at C-O stretch - 1260-1000 cm^{-1} O-H stretch - 3400-3300 cm^{-1}, Alkanes at C-H stretch - 2950-2800 cm^{-1}

In formulation (Tablets) Infra Red Spectrum the peaks and the functional groups are found to be Amides at C=O Stretching –1637.72 cm^{-1},carboxylic Acid at C-O Stretching – 1260.73cm^{-1}, O-H Bending – 1423.46 cm^{-1},Amines at N-H stretch – 3400.65 cm^{-1}, Alcohols at C-O stretch – 1260.73 cm^{-1},Alkanes at C-H stretch - 2914 cm^{-1}.The IR spectrum peaks of functional groups were noted and then the functional groups of API and that of excipients were identified and then the IR values are identified and compared with that of the spectrum that is obtained with the standard values and showed in the figures 1 and 2 that there is no interaction between the API and excipients.

Micromeritic Properties of Powder Blend

The powder mixtures of different formulations were evaluated for angle of repose, bulk density, Hausner's ratio, compressibility index and their values were shown in Table 6. The results of angle of repose (< 40) and compressibility index (< 22) indicates fair to passable flow properties of the powder mixture. All tablet formulations was found to be within the limit.

Physical Parameters
Strategy I

The first strategy was to develop a formulation based on innovator composition. The direct compression technique formulation (F2) resulted in segregation and finally led to poor content uniformity, assay on lower side, poor flowability as carr's index was 36.36, so the wet granulation is preferred.

The wet granulation technique formulation (F2) ultimately led to formulation that has met all the requirements needed for a sublingual formulation. The Physical parameters were found to be within the limits and in-vitro drug release, assay values are also within the limits. Finally better content uniformity was achieved with the wet granulation technique. Now this formulation (F2) is taken as reference trial for developing the generic version avoiding all the patent issues.

The Dissolution Studies are also satisfactory for the innovator trials.
Strategy II:-The second strategy was developed by using the combination of Microcrystalline Cellulose & Mannitol. In this strategy, the formulation F3 was developed by

direct compression by using Avicel pH 101 & Pearlitol SD100 along with superdisintegrants combination of croscarmellose sodium and low substituted hydroxypropyl cellulose. Even the formulation has content uniformity the assay was found on the lower side, poor flowability and higher disintegration time. So, the next plan was to shift for wet granulation formulation (F4).

The wet granulation formulation (F4) resulted in good content uniformity, assay values are in limits, but has poor flowability and also slightly higher disintegration time that is not a desired character for developing the generic version of innovator formulation as innovator formulation has disintegration time of less than 12 seconds.

The next formulation was developed by direct compression, this time by eliminating low substituted hydroxyl propyl cellulose and the diluents used are the combinations of Pearlitol SD200 and Prosolve SMCC 90 (Silcified MCC). This formulation (F5) resulted in poor flowability, assay was found to be on lower side and also poor content uniformity.

The above formulation design was changed to wet granulation and new formulation (F6) was developed. In this formulation, the diluents combinations are pearlitol 160C and pearlitol SD200 along with silicified MCC (Prosolve SMCC 90).This formulation although has good content uniformity and assay value within the limit, but has poor flowability and also slightly higher disintegration time.

A new formulation (F7) was designed by incorporating buffering agents to the above formulation and evaluated for all the parameters. The flowability was improved but the disintegration time was increased which is not a desired character for developing the generic version for the innovator drug. All the formulations have satisfactory drug release within 30 minutes of dissolution studies.

Strategy III:-The next strategy was developed by using F-melt as diluent to improve the flowability and maintaining the content uniformity. The F8 formulation was developed by direct compression and evaluated for the physical parameters and it was found that the flow property was improved but the content uniformity was not good, so wet granulation was preferred and new formulation was designed.

The F9 formulation was made by wet granulation technique and evaluated for physical parameters and the flow property was improved along with content uniformity, but has slightly higher disintegration time, so the next formulation was designed in such a way that disintegration time has to be improved by increasing the superdisintegrtant concentration and final reproducible batch was taken and evaluated for all the physical parameters, assay and content uniformity.

The final reproducible batch (F10) was found to have good flow properties, content uniformity and assay was found to be within limits. The dissolution studies also correlated with that of the innovator drug. All this physical characters are explained in table 7.

Water Absorption Ratio

The physical evaluation of water absorption was explained in the table 8 it is in the range of 33.59 for the formulation 9 and 96.40 for the formulation 6.

Dissolution Studies

The in vitro dissolution studies were explained as shown in the table 9 and figure 3. From all formulation F10 will be the best generic preparation that can be made available to commercialize in the market avoiding all the patent issues by comparing with the innovator.

Stability Studies

The stability studies of all the optimized formulation are done and are explained as shown in the table 10.

Strategy I

Table 1. Formulation Design of F1, F2

Ingredients	F1(mg/tablet)	F2(mg/tablet)
Zolpidem Tartrate	3.54	3.54
Pharmaburst®500	68.21	67.71
Crosscarmellose Sodium	4.50	3.50
PVP K30	-	1.50
Sodium Carbonate	8.00	8.00
Sodium Bicarbonate	11.00	11.00
Syloid 244 FP(Colloidal Silica)	1.50	1.50
Sucralose	0.25	0.25
Peppermint Flavour	0.25	0.25
Yellow Iron Oxide	0.25	0.25
Sodium Stearyl Fumarate	2.50	2.50

Strategy II

Table 2. Formulation Design of F3, F4

Ingredients	F3(mg/tablet)	F4(mg/tablet)
Zolpidem Tartrate	3.54	3.54
Avicel PH 101	25.00	-

Avicel PH 102	-	30.96
Pearlitol SD 100 (Mannitol)	59.46	54.00
L-HPC	3.00	-
Crosscarmellose Sodium	3.00	4.00
PVP K30	-	1.50
Colloidal Silica	2.50	2.50
Sucralose	1.00	1.00
Peppermint Flavour	0.25	0.25
Yellow Iron Oxide	0.25	0.25
Sodium Stearyl Fumarate	2.00	2.00

Table 3. Formulation Design of F5, F6, F7

Ingredients	F5(mg/tablet)	F6(mg/tablet)	F7(mg/tablet)
Zolpidem tartrate	3.54	3.54	3.54
Prosolve SMCC90	25.00	25.00	20.00
Pearlitol SD200	61.96	29.00	24.75
Pearlitol 160C	-	31.46	30.46
Croscarmellose Sodium	3.50	3.50	4.50
PVP K30	-	1.50	1.50
Buffering Agents	-	-	10.00
Aerosil 200 (Colloidal Silica)	2.50	2.50	2.50
Sucralose	1.00	1.00	0.25
Peppermint Flavour	0.25	0.25	0.25
Yellow Iron Oxide	0.25	0.25	0.25
Sodium Stearyl Fumarate	2.00	2.00	2.0

Strategy III

Table 4. Formulation Design of F8, F9, F10

Ingredients	F8(mg/tablet)	F9(mg/tablet)	F10(mg/tablet)
Zolpidem Tartrate	3.54	3.54	3.54
F-Melt	88.46	75.21	76.71
Crosscarmellose Sodium	-	4.00	4.50
PVP K30	-	1.50	1.50
Buffering Agents	-	10.00	8.00
Colloidal Silica	3.50	2.50	2.50
Sucralose	1.50	0.25	0.25
Yellow Iron Oxide	0.50	0.25	0.25
Peppermint Flavour	0.50	0.25	0.25
Sodium Stearyl Fumarate	2.00	2.50	2.50

Table 5. Preformulation Studies of Physical Mixture of API & Excipients.

Sample	Initial	1 M, 40°C/75% RH
	% Impurity	% Impurity
API + F Melt	Not Detected	Not Detected
API+ Sodium Bicarbonate	Not Detected	Not Detected
API + Lactose	0.004	0.004
API + Peppermint	Not Detected	0.03
API + Mannitol	Not Detected	Not Detected
API + Silcified MCC	Not Detected	Not Detected
API + Sucralose	Not Detected	Not Detected
API + Sodium Stearyl Fumarate	Not Detected	Not Detected
API + Yellow Iron Oxide	Not Detected	Not Detected
API + Silicon Dioxide	Not Detected	Not Detected
API + Croscarmellose Sodium	Not Detected	Not Detected
API + L-HPC	Not Detected	Not Detected
API + Sodium Carbonate	Not Detected	Not Detected
API + PVP K-30	0.003	0.003
API + MCC	Not Detected	Not Detected
API + Pharmaburst	0.003	0.003

Table 6. Micromeritic Properties of powder blend

Formulation code	Parameters						
	Bulk Density	Tapped Density	Carr's Index	Hausner's Ratio	Flow Property	Angle of repose	Flow Property
F1	0.44	0.6	36.36	1.36	Very Poor	33.06	Good
F2	0.46	0.51	10.86	1.1	Good	28.8	Excellent
F3	0.49	0.66	34.69	1.34	Very Poor	32.2	Good
F4	0.44	0.59	34.09	1.34	Very Poor	30.96	Good
F5	0.54	0.8	48.14	1.48	Very Poor	30.96	Good
F6	0.42	0.63	50	1.5	Very Poor	29.2	Excellent
F7	0.43	0.5	16.27	1.16	Fair	27.6	Excellent
F8	0.43	0.52	20.93	1.2	Passable	32.6	Good
F9	0.45	0.51	13.33	1.13	Good	30.5	Good
F10	0.44	0.51	15.9	1.15	Good	29.6	Excellent

Table 7. Physical parameters evaluation Observations

Formulation code	Parameters								
	Hardness (Newtons)± SD	Thickness (mm) ± SD	Disintegration Time (Seconds)± SD	Friability (%)	pH	Wetting Time (seconds)	Average Weight of 20 Tablets± SD	Content uniformity ± SD	Assay (%)
F1	34±1	2.41±0.03	10.8±0.83	0.11	6.70	11.6	100.73±0.92	85.96±2.27	86.3
F2	29±1.41	2.33±0.01	11.4±1.14	0.09	10.38	50.8	100.76±1.03	98.5±5.09	98.6
F3	29.8±1.78	2.53±0.01	14.8±1.48	0.21	6.77	35.8	100.75±1.19	91.3±7.07	94.3
F4	25±1.41	2.48±0.01	15.2±1.30	0.13	6.63	46	100.80±1.24	101.58±2.19	90.9
F5	31±1	2.46±0.01	11.4±1.14	0.25	6.58	20.2	100.99±1.24	79.5±8.66	76.6
F6	31.4±0.89	2.36±0.008	16.2±1.30	0.19	6.78	37.4	100.94±1.26	100.18±2.90	98.3
F7	24.2±1.09	2.36±0.01	21.2±1.30	0.29	10.68	35.4	101.03±1.32	103.1±1.89	103
F8	32.8±2.28	3.43±0.008	17.6±1.81	0.1	6.02	34.2	100.97±1.30	94.58±1.82	86.9
F9	29±1.41	3.53±0.01	13.8±1.30	0.17	10.34	54.2	100.97±1.32	98.5±6.49	97.7
F10	24.6±1.34	2.42±0.008	12.3±1.30	0.1	10.31	51.6	101.09±1.38	95.4±1.27	100.1

Table 8. Water Absorption Ratio Observations

Strategy	Formulation code	Parameters		
		Initial weight(mg)	Final weight(mg)	Water absorption ratio
Strategy I	**F1**	101.91	178.28	74.93
	F2	102.74	162.06	57.7
Strategy II	**F3**	101.50	181.23	78.55
	F4	101.65	175.45	72.60
	F5	102.50	167.34	82.77
	F6	101.81	199.96	96.40
	F7	101.34	189.34	86.83
Strategy III	**F8**	101.56	182.06	79.26
	F9	102.80	137.34	33.59
	F10	102.13	165.83	62.37

Table 9. Dissolution Results

Strategy	Formulation code	% Drug Release With Time(Minutes)						
		1	3	5	7	10	15	30
Strategy I	**F1**	57.4±6.33	66.8±4.93	71.7±4.26	74.2±4.19	77.5±3.86	80±3.20	82.9±2.58
	F2	45.7±3.44	71.6±3.23	78.8±2.97	81.9±2.34	84.5±2.12	87±1.98	95.4±1.87
Strategy II	**F3**	51.1±3.35	66.3±3.44	81.1±2.44	85.2±2.34	88.7±2.30	90.4±1.96	94.3±1.82
	F4	26.7±3.77	51.6±3.45	67.5±3.12	74.3±2.54	81.9±2.58	86.7±2.23	92.3±1.93
	F5	59.9±3.54	69.4±3.23	73.6±3.22	75.1±2.78	77.3±2.58	79.4±2.33	81.9±2.08
	F6	64.7±2.88	87.8±2.74	91.4±2.33	92.8±2.12	94±1.87	95.3±1.56	96.9±1.34
	F7	51.6±2.56	60.4±2.43	70.3±2.58	77.6±2.23	84.2±1.56	89.8±1.34	93.1±1.23
Strategy III	**F8**	81.2±2.64	86±2.23	86.6±2.12	89.6±1.88	91.3±1.54	92.7±1.78	95.3±1.34
	F9	49.2±2.42	73.6±2.12	81.4±1.89	85.4±1.73	88.8±1.56	91.8±1.45	95.6±1.33
	F10	49.3±2.12	77.7±1.98	84.1±1.67	86.8±1.77	89.4±1.56	92.5±1.34	94.9±1.15

Table 10. Stability Studies of Formulation F10

Time in Days	% Drug Content					
	Room Temperature			40±2°C/75%±5% RH		
	F2	F7	F10	F2	F7	F10
0	99.23	98.43	98.93	99.23	98.43	98.93
30	99.17	98.27	98.72	98.69	98.09	98.62
60	98.89	97.89	98.59	98.62	97.52	98.32
90	98.73	97.63	98.23	98.50	97.07	98.06

Fig 1. a) FT-IR Graph of API b) FT-IR Graph of L-HPC + Croscarmellose Sodium+MCC+Mannitol c) FT-IR Graph of Croscarmellose Sodium+MCC+Mannitol+PVP K30 d) FT-IR Graph of Croscarmellose Sodium+MCC+Mannitol+Buffering agents+ PVP K30

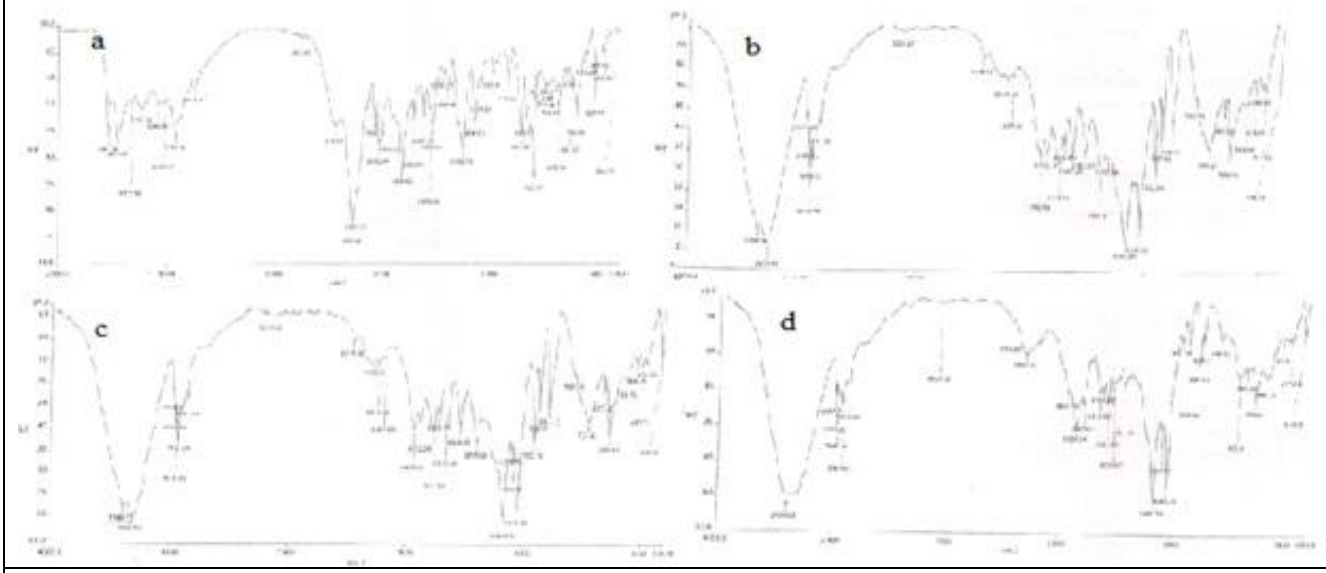


Fig 2. e) FT-IR Graph of F-Melt+Croscarmellose Sodium+Buffering agents+ PVP K30 f) FT-IR Graph of API+ L-HPC+Croscarmellose Sodium+ MCC+Mannitol g) FT-IR Graph of API+ Croscarmellose Sodium+MCC+Mannitol+PVPK30 h) FT-IR Graph of API+ Croscarmellose Sodium+MCC+ Mannitol+Buffering agents+ PVP K30 i) FT-IR Graph of API+ F-Melt + Croscarmellose Sodium + Buffering agents + PVP K30

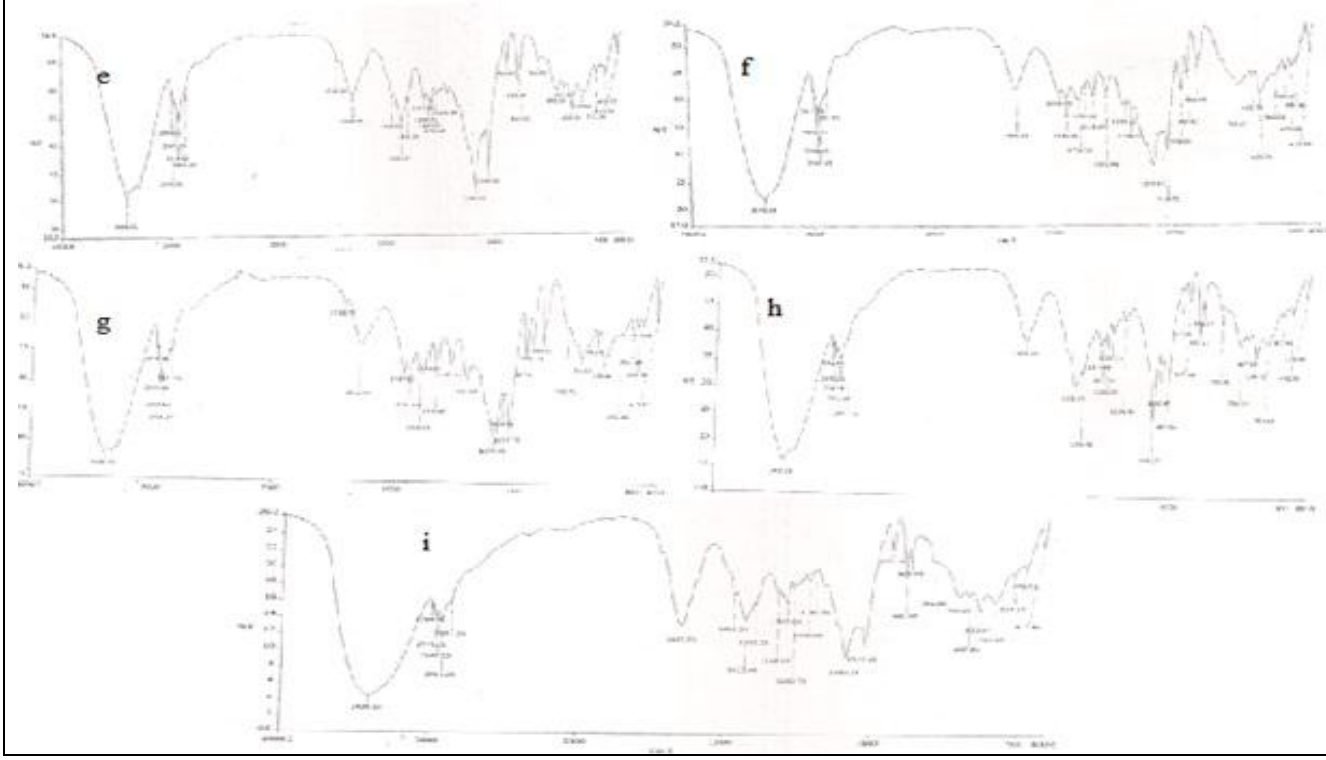
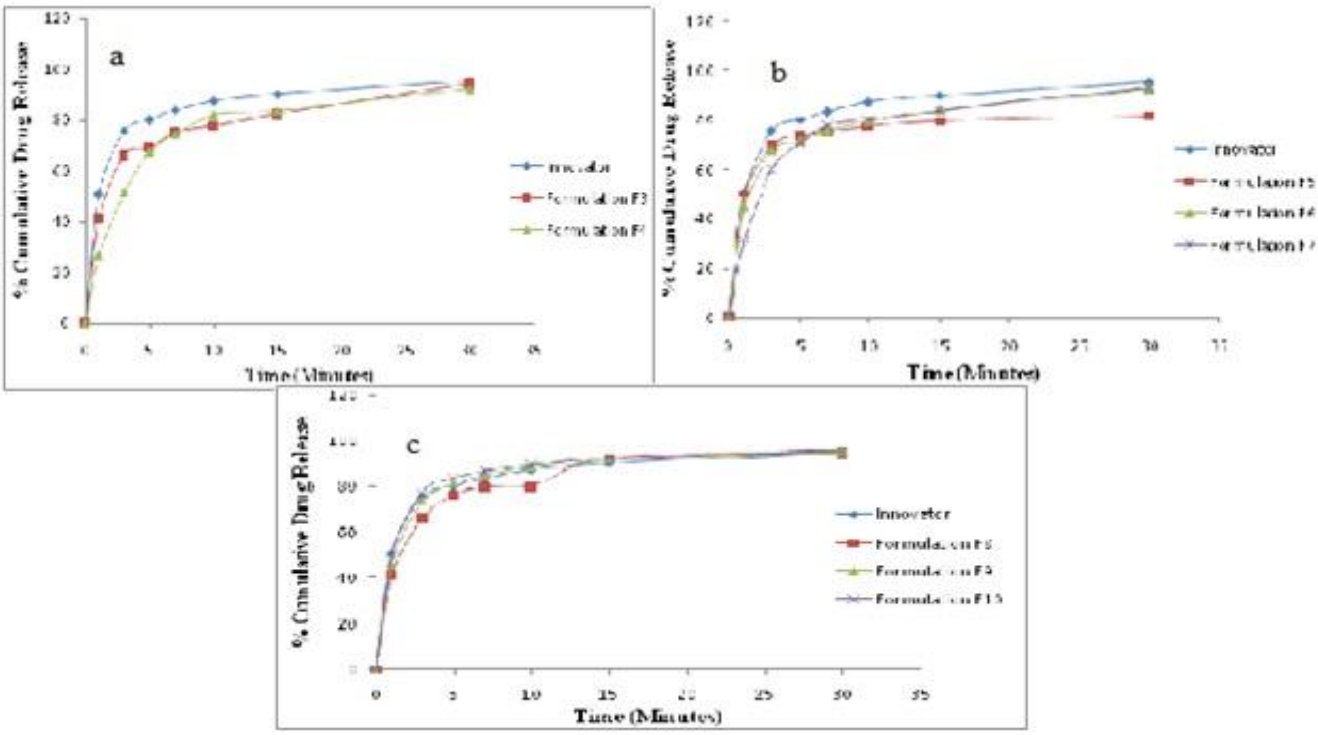


Fig 3. a) Comparison of Dissolution Profile of Formulations F3 & F4 with the innovator drug profile b) Comparison of Dissolution Profile of Formulations F5, F6 & F7 with the innovator drug profile c) Comparison of Dissolution Profile of Formulations F8, F9 & F10 with the innovator drug profile



CONCLUSION

The generic version of INTERMEZZO® sublingual tablets of 3.5mg strength was successfully prepared by using buffer system of Sodium Carbonate and Potassium Bitartrate. The final optimized formulation F10 was evaluated for all physical parameters and *in-vitro* drug release. The optimized formula F10 is the best competitive generic version for the Innovator formulation. All the physical evaluation parameters and in-vitro drug release patterns are found to compete with that of the innovator preparation and also faster disintegration time was achieved with the optimized formula that competes with the innovator formulation.

Although all the physical parameters and in-vitro drug release patterns are competitive with the innovator preparation showing the bioequivalence is an important scenario in order to be prove more competitive generic version of INTERMEZZO®. Therefore, Bio equivalence tests should be conducted and then only we can assure that the final optimized formula F10 will be the best generic preparation that can be made available to commercialize in the market avoiding all the patent issues.

REFERENCES

1. Allen A. The gastrointestinal physiology: Salivary, gastric and hepatobiliary secretions, Handbook of Physiology, American Physiological Society, Bethesda, MD, 3(6), 1989, 359-382.
2. Allen LV. Featured excipient: capsule and tablet diluents. *International Journal of Pharmaceutical Compounding*, 4(4), 2000, 306–310, 324–325.
3. Allen LV. Rapid dissolve technology - an interview. *International Journal of Pharmaceutical Technology*, 7, 2003, 449-445.
4. Amir HS, Senlin Z, Xiaoling L, Transbuccal Delivery of Acyclovir (II) - Feasibility, System Design and In Vitro Permeation Studies. *Journal of Pharmaceutical Sciences*, 1998, 1(2), 66-73.
5. Anderson NR *et al*., Quantitative evaluation of pharmaceutical effervescent systems I: - design of testing apparatus. *Journal of Pharmaceutical Sciences*, 71(1), 1982, 3–6.
6. Bala R, Seth N, Yogesh B, Shailesh S. *International Research Journal of Pharmacy*, 1(1), 2010, 417-427.
7. Boer D *et al*., Drug absorption by sublingual and rectal routes. *British Journal of Anaesthesia*, 56, 1984, 69-82.
8. Bolton S, Atluri R. Crystalline sorbitol tablets - effect of mixing time a lubricants on manufacturing. *Drug Cosmetic Industry Magazine*, 135(5), 1984, 44, 46, 47, 48, 50.
9. Botzolakis JE, Augsburger LL. Disintegrating agents in hard gelatin capsules, Part I: mechanism of action. *Drug Development and Industrial Pharmacy*, 14(1), 1988, 29–41.
10. Bouffard J *et al*., Influence of processing variables and physicochemical properties on the granulation mechanisms of mannitol in a fluid bed top spray granulator. *Drug Development & Industrial Pharmacy*, 31, 2005, 923–933.

11. Brahmankar DM, Jaiswal SB. Biopharmaceutics & Pharmaceutics - A Treatise, 2nd , ed., 2009, 6.
12. Bures P, Huang Y, Oral E, Peppas NA. Surface modifications and molecular imprinting of polymers in medical and pharmaceutical applications. *Journal of Controlled Release*, 72, 2001, 25-33.
13. Castellanos MR, Zia H, Rhodes CT. Mucoadhesive drug delivery systems. *Drug Development and Industrial Pharmacy*, 19, 1993, 143-194.
14. Cervera MF *et al*., Solid state and mechanical properties of aqueous chitosan-amylose starch films plasticized with polyols. *AAPS Pharmaceutical Science & Technology*, 2004, 5(1), E15.
15. Chasseaud LF, Darragh ED, Lambe RF, Taylor T. Isosorbide dinitrate plasma concentration and bioavailability in human subjects after administration of standard oral and sublingual formulations. *Journal of Pharmaceutical Sciences*, 1984, 73(5), 699-701.
16. Collins LMC, Dawes C. The surface area of adult human mouth and thickness of salivary film covering the teeth and oral mucosa. *Journal of Dental Research*, 1987, 66, 1300-1302.
17. Consuelo ID, Jacques Y, Pizzolato G, Guy RH, Falson F. Comparison of the lipid composition of porcine buccal and esophageal permeability barriers. *Archives of Oral Biology*, 50, 2005, 981-987.
18. Cummings JH, Banwell JG, Segal I, Coleman N, Englyst HN, Macfarlane GT. The amount and composition of large bowel contents in man. *Gastroenterology*, 98, 1990, A408.
19. Dahl TC *et al*., The influence of disintegrant level and capsule size on dissolution of hard gelatin capsules stored in high humidity conditions. *Drug Development and Industrial Pharmacy*, 17(7), 1991, 1001–1016.
20. Daoust RG, Lynch MJ. Mannitol in chewable tablets. *Drug Cosmetic Industry*, 93(1), 1963, 26–2888, 92, 128–129.
21. David JG, Marcia D, Jerold SH and Richard IS. Pharmacokinetic comparison of sublingual Lorazepam with Intravenous, Intramuscular, and oral Lorazepam. *Journal of Pharmaceutical Sciences*, 71(2), 1982, 248-252.
22. De Felippis MR. Overcoming the challenges of noninvasive proteins and peptides delivery. *American Pharmacy Review*, 6, 2003, 21-30.
23. De Vries ME, Bodde HE, Verhoef JC, Junginger HE. Developments in buccal drug delivery. *Critical Reviews in Therapeutic Drug Carrier System*, 8, 1991, 271-303.
24. Debord B *et al.*, Study of different crystalline forms of mannitol - comparative behaviour under compression. *Drug Development & Industrial Pharmacy*, 1987, 13, 1533–1546.
25. Deneer VHM, Drese GB, Roemele PEH, Verhoef JC, Lie-A-Huen L, Kingma JH, Brouwers JRBJ, Junginger HE. Buccal transport of flecainide and sotalol: effect of a bile salt and ionization state. *International Journal of Pharmaceutical Sciences*, 241, 2002, 127-134.