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FORMULATION AND EVALUATION OF MOUTH DISSOLVING FILM OF CHLORPHENIRAMINE MALEATE

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ABSTRACT
Aim of present study was to develop mouth dissolving filmt that disintegrates rapidly in mouth by using tasteless drug resin complex (DRC) of Chlorpheniramine maleate (CPM) using Tulsion-335 as ion exchange resin. Formulated drug resin complex was evaluated for by taste and percentage drug loading. Formulated DRC was characterized by infrared spectroscopy. Different batches were developed using optimized DRC by solvent casting method. *In vitro* release of CPM from formulation in simulated salivary fluid was more than 95% within 2 minutes. Taste masking and *in vivo* disintegration were in acceptable range. Among different batches F1 batch was found suitable with drug-resin complex to get the low disintegration time along with good physicomechanical properties. These results indicated that the disintegration and drug release of CPM can be increased to a greater extent by optimizing various formulation variables in formulation.

KEYWORDS: Chlorpheniramine maleate, Tulsion 335, Kyron T 314, Poly ethylene glycol.

INTRODUCTION
Taste masking is defined as a perceived reduction of an undesirable taste that would otherwise exist. The ideal solution to reduce or inhibit bitterness is the discovery of a universal inhibitor of all bitter tasting substances that does not affect the other taste modalities such as sweetness or saltiness.Many techniques have been developed which have not only improved the taste of product, but also the stability of the formulation & performance of the product. In numerous cases, the bitter taste modality is an undesirable trait of the product or formulations and can considerably affect its acceptability by consumers.[1,2]

Ion exchange resins are synthetic inert organic polymers consisting of a hydrocarbon network to which ionisable groups are attached and they have the ability to exchange their labile ions for ions present in the solution with which they are in contact.[3-4]

The most frequently employed polymeric network used is a copolymer of styrene and divinylbenzene (DVB). Apart from this other polymers such as those of acrylic and methacrylic acid cross linked with DVB and containing appropriate functional groups, have been used as ion exchange drug carriers.[5-6]

Chlorphenamine, also known as chlorpheniramine, is an antihistamine used to treat the symptoms of allergic conditions such as allergic rhinitis. Chlorpheniramine maleate appears as odorless white crystalline solid or white powder with a bitter taste.[7]

In present study an attempt was made to mask the taste of CPM with formulation of mouth dissolving film having desired good characteristics so as to give pleasant taste, good bioavailability along with improved patient compliance.

MATERIALS AND METHODS
Materials
Chlorpheniramine maleate, Tulsion 335 and Kyron T 314 was received as gift sample from Geneka Healthcare, Haridwar, India. Polyethyle glycol was purchased from S.D. Fine Chemical, India. Aspartame, Vailline and amaranth was purchased from Hitech India limited, India. All the ingredients of analytical grade were used.

Melting point determination of CPM
Capillary tube was filled with CPM and placed in the melting point apparatus. Apparatus was set at a high enough level to make a rapid determination of melting point. The melting process of CPM was observed though the magnifying lens to determine the melting point.

Calibration graphs preparation in Phosphate buffer pH 6.8

Pure drug of CPM (100mg) was accurately weighed and transferred to 100 ml of volumetric flask. Drug was dissolved in phosphate buffer 6.8 and volume was made up to 100 ml. The concentration of drug was 1000 µg/ml.

Calibration curve of pure drug

Standard solution was prepared by dissolving 100mg of CPM in a 100 ml of volumetric flask and this solution was made up to the mark with water. From the standard solution of CPM was subsequently diluted with water to obtain a series of dilutions containing 20-100 µg/ml of CPMin 1 ml solution. The absorbance of these solutions was measured at 261 nm UV spectrophotometer (JASCOV530) against corresponding blank. The concentration of CPM and the corresponding absorbance values are given in table 5. The calibration curves for the estimation of CPM were constructed by plotting linear best fit between concentration of CPM and corresponding mean absorbance value.

Identification of CPM using FTIR spectra

FTIR study was carried out to check purity of drug. It was determined by Fourier Transform Infrared spectrophotometer (Jasco-FTIR 4100). The baseline correction was done by blank background measurement. The scanning range was 400-4000 cm^{-1}.[8]

Activation of Cationic Ion Exchange Resins

Ion exchange resin (Tulsion 335) was placed on a whatman filter paper in a funnel and was washed with deionised water. The resins was activated by 50 mL of 1N HCl followed by washing with deionised water, until neutral pH of filtrate was achieved and dried overnight in hot air oven at 50°C and was stored in an air tight glass vial.[10]

Preparation of DRCs

Drug resin complex was prepared by batch process, keeping the quantity of drug constant. Different ratios of drug:ion exchange resins (tulsion335) was selected (1:1, 1:2, 1:3 and 1:4). Resin was then allowed to swell in 20 mL water under magnetic stirring at room temperature for 30 min. After 30 min, drug was added to swelled resin slurry under magnetic stirring. The resultant mixture was stirred again for 1 h at room temperature. The drug-resin complex was separated by filtration and residue was washed with de-ionised water to remove any uncomplexed drug, and dried in hot air oven at 50°C. The complex was then stored in an air tight glass vial.[9]

Evaluation of drug–resin complex

Assessment of the bitter taste of drug (bitterness threshold)

The bitter taste threshold value of CPM was determined based on the bitter taste recognized by six volunteers. Before measurement, informed written consent was taken from each volunteer. Various concentrations (10-100 µg/ml) of drug were prepared in phosphate buffer pH 6.8. Mouth was rinsed with buffer solution and then, 10 ml of the most diluted solution was tasted by swirling it in the mouth mainly near the base of the tongue for 30 s. If the bitter sensation was no longer felt in the mouth after 30 s, the solution was spat out and waited for 1 min to ascertain whether this is due to delayed sensitivity. Then the mouth was rinsed with safe drinking water. The recording was '-', means did not detect any difference in taste; '+' means detected some difference but was not able to be specify about the taste and '++' means detected a bitter taste. The next highest concentration was tasted after a time gap of 10 min. The threshold of bitterness of the drug is defined as the concentration at which more than half of the volunteer's detected bitterness when holding the drug or formulation in their mouth. The threshold value was correspondingly selected from the different drug concentrations as the lowest concentration that had a bitter taste.

Percent drug loading

Aliquots from DRC was withdrawn and filtrates was then be analyzed by UV spectrophotometry for unbound drug in triplicate.

Drug Content

A complex equivalent to 25 mg was accurately weighed and 10 mL of 1N HCl was added to break the drug resin complex, under continuous stirring for 2 min. Solution was then be filtered and absorbance was measured at 261 nm using UV-spectrophotometer the readings was taken in triplicate.[10]

Formulation Development of Mouth Dissolved Film of taste masked complex of Chlorpheniramine Maleate

DRC containing films were fabricated by the solvent casting method (Table 1). Different amount of xanthan gum was dissolved in 5ml of water and stirrer continuously for 1 hour, optimized amount of Plasticizer (0.5%) was then dissolved in 95% ethanol and then added to the polymeric solution, the optimized amount of drug was dissolved in 2ml of water and kept on sonication for proper dispersion. Polymeric solution was stirred for 30 min using magnetic stirrer and was kept in undisturbed condition till the entrapped air bubbles removed. The aqueous solution was casted in a glass moulds having 2.5 x 2.5 cm*12 films area and was dried at controlled room temperature (25°-30°C, 45%RH) as well as at increased temperature (microwave oven). The film was dried at controlled room temperature. The dried film was carefully removed from the glass plates and was cut into the size required for testing. The film was stored in air tight plastic bags till further use.

Table 1: Composition of fast dissolving films of taste masked complex of CPM using Xanthan gum (F1-F5).

INGREDIENTS	FORMULATION				
Formulation code	F1	F2	F3	F4	F5
DRC equivalent to 25mg	50	50	50	50	50
Xanthan gum (mg)	20	30	40	50	60
Poly ethylene glycol 400(ml)	0.5	0.5	0.5	0.5	0.5
Kyron T 314	10	10	10	10	10
Citric acid (mg)	5	5	5	5	5
Sucrose(mg)	5	5	5	5	5
Falvor (mg)	qs	qs	Qs	qs	qs
Amaranth (mg)	qs	qs	Qs	qs	qs
Water (ml)	10	10	10	10	10

Evaluation of Prepared Film

Thickness

Randomly 10 films were selected and thickness was measured using digital vernier calliper at three different places.

Weight variation

For weight variation test, 10 films from each batch were weighed individually by digital electronic balance and the average weight was then being calculated.

Folding endurance

This was determined by repeatedly folding one film at the same place until it broke. The number of times the film could be folded at the same place without breaking cracking gave the value of folding endurance.[11]

Percentage of moisture content

The films was weighed individually and kept in desiccators containing activated silica at room temperature for 24 hrs. Individual films were weighed repeatedly until they showed a constant weight. The percentage of moisture content was then be calculated as the difference between initial and final weight with respect to final weight.

Drug content analysis

The films of specified area was taken into a 10 ml volumetric flask and dissolved in methanol and volume was made up with 10 ml methanol. Subsequent dilutions was made and analyzed by UV spectrophotometer at 261.6nm.

Disintegrating time

The most important criteria of present work are to that dosage form should be dissolved within few seconds. The incorporation of super disintegrating agent to minimizes the disintegrating time. The film of specific size (unit dose) was placed on a petridish containing 10 ml of distilled water. The time required for the film to break was noted as cursive *in vitro* disintegration time.[12]

***In vitro* dissolution study**

In vitro drug release studies were performed by using Franz diffusion cell with dialysis membrane. It consists of a donor compartment and a receptor compartment. The receptor compartment was filled with 20ml of

phosphate buffer solution as a diffusion medium. The prepared film was taken in the receptor compartment the medium was continuously stirred at 50 rpm using magnetic beads and the temperature was maintained at 37±1˚C. 1ml sample of receptor fluid was withdrawn at predetermined intervals and volume was replaced with same volume of 1ml phosphate buffer solution the sample analyzed spectrophotometrically at 261 nm using JASCO V 530.The cumulative amount of drug permitted was calculated and plotted against time.[13]

RESULTS AND DISCUSSION

Melting point determination

Melting point of CPM was found as 131^{o}C which was similar to standard vale of, 130-135 ºC. The observed value is very close to the standard value. This indicates purity of drug.

Calibration curve of pure drug

The calibration curves for the estimation of CPM were constructed by plotting linear best fit between concentration of CPM and corresponding mean absorbance value are shown in table 2 & figure 1.

Table 2: Estimation of CPM measured at in phosphate buffer (pH 6.8) using UV Spectrophotometry.

S. No.	Concentration (µg/ml)	Absorbance
1	20	0.210
2	40	0.402
3	60	0.599
4	80	0.798
5	100	0.996

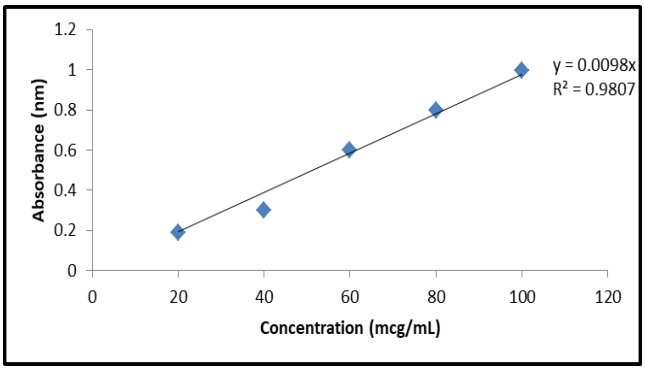

Figure 1: Estimation of CPM measured in phosphate buffer (pH 6.8) using UV Spectrophotometry.

FTIR Spectra

IR spectra of drug in KBr pellets at moderate scanning speed between 4000-400 cm^{-1} was carried out using FTIR (Jasco FTIR 6100 type A). The spectrum is shows in figure-2. The peak values (Wave number (cm-^{1}).

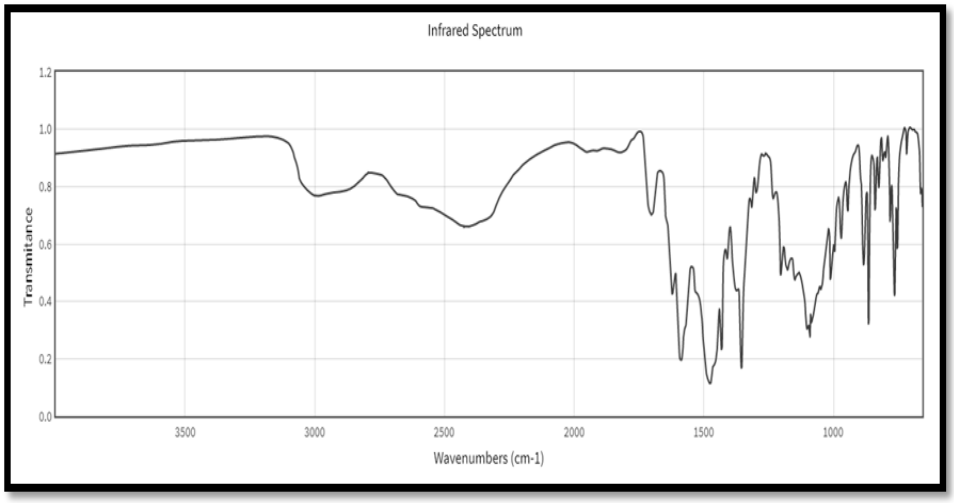

Figure 2: FTIR spectra of pure drug of Chlorpheniramine Maleate.

Percent drug loading

Percent drug loading was found in between 40.70±0.5 to 97.33±0.34% as shown in table 3. Drug loading of formulation batch DRC2 was found 97.33%

Drug Content

Drug content of all the batches of DRC was observed and found in range of 96.45±1.21 to 99.54±1.0 %. as shown in table 3. As the percent drug loading and drug content was found highest in batch DRC2 which was further used to develop mouth dissolving films.

Table 3: Characterization of Drug resin complex of CPM

Batch	Drug: Resin ratio	Swelling Time (Min)	Stirring Time (Min)	Taste	pH	% Drug Loading	Drug content (%)
DRC1	1:1	40	240	++	5.78	89.33±1..02	97.65±0.15
DRC2	1:2			+++	5.18	97.33±0.34	99.54±1.0
DRC3	1:3			+++	6.69	90.28±1.05	96.45±1.21
DRC4	1:4			+++	5.86	94.70±0.50	97.77±1.11

All batches contained 25 mg of CPM, +++ Complete taste masking

Evaluation of films

FTIR spectrometry

The FTIR spectrum of pure CPM and optimized formulation are shown in figure 3. In order to determine possible interaction between drug with carrier, FTIR was used. The CPM shows characteristic peak of N-H stretching vibration at 2350.92cm^{-1} , C=O stretching 1697.92 cm^{-1}, C=N stretch 1576.97 cm^{-1}, Carboxylate 1353.31 cm^{-1} and Maleate 860.78 cm^{-1}. The FTIR spectra of optimized formulation showed same peak as that of pure drug CPM. From FTIR spectra it was observed that there was no any incompatibility between drug and excipients.

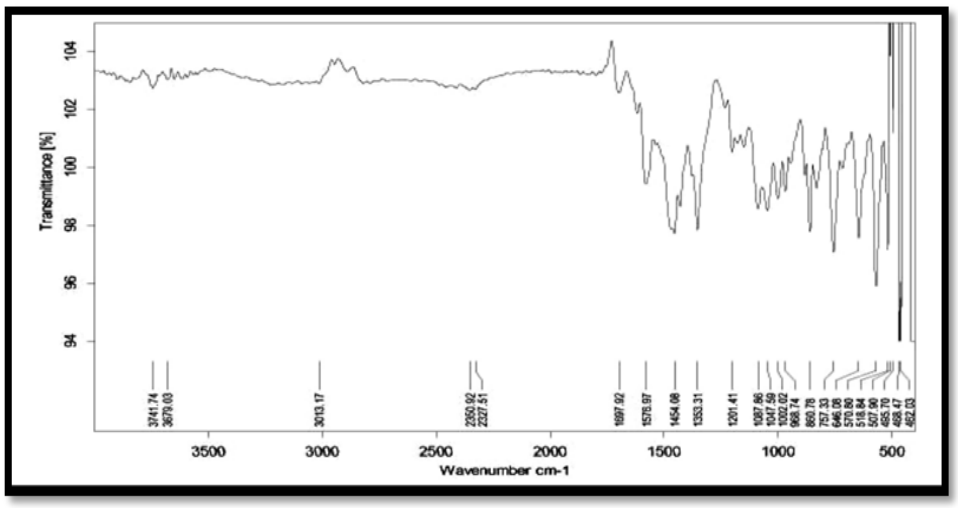

Figure 3: FTIR spectra of DRC containing MDF.

All the formulated films were observed as non sticky, soft and semi transparent. Surface of all the formulation was observed smooth. Weights of all formulations were found uniform.

Thickness

The thickness of all formulations F1- F15 was found by using digital micrometer and the results were shown in the table 4.

Table 4: Determination of thickness for Different formulations of CPM films (F1-F5)

S. No.	Formulation	Thickness (µm)± SD
1	F1	101±2.5
2	F2	105±3.5
3	F3	104±2.5
4	F4	106±1.0
5	F5	107±0.3

The thickness of F1 to F5 was found to be 98-105µm. From the results obtained from the above formulations, all formulations showed thickness of films as 5-200µm and complies with the limit as per the previous value. It is observed that as the concentration of xanthan gum was increases thickness of the film increases.

Folding endurance

Folding endurance was determined by repeatedly folding a small strip of film at the same place till it break. The folding endurance value of F1 to F5 was found to be 65-105 as shown in table 4. It was observed that folding endurance decreases with increase in the concentration of polyme r.

Table 5: Determination of folding endurance for Different formulations of CPM films (F1-F5).

S. No.	Formulation	Folding Endurance
1	F1	105
2	F2	95
3	F3	90
4	F4	80
5	F5	65

Surface pH of films

The surface pH of films was determined to investigate the possible side effect because of change in pH in vivo, since an acidic or alkaline pH may cause irritation to oral mucosa. The surface pH of all the formulation was found to be in the range of 6.8-7.2 and hence will not cause any irritation to oral mucosa (Table 6).

Table 6: Determination of Surface pH for Different formulations of CPM films (F1-F5).

S.No.	FORMULATION	SURFACE pH
1	F1	6.84±0.05
2	F2	6.75±0.01
3	F3	7.03±0.12
4	F4	7.00±0.08
5	F5	6.95±0.05

Disintegration test (USP 2007)

Disintegration test for all prepared formulations was carried out using disintegration test apparatus as prescribed in USP 2007. F1-F5 showed a disintegration time of 30-46 seconds as shown in table 7 & figure 4. From the results obtained, by increasing the concentration of polymer, disintegration time was increased. Formulation F1 observed to give minimum disintegration time 30 sec as compared to other formulations hence F1 can be lead to develop CPM as fast dissolving delivery system.

Table 7: Determination of disintegration time for different formulations of CPM films (F1-F5).

S.No.	FORMULATION	Disintegration time (seconds)
1	F1	30
2	F2	38
3	F3	41
4	F4	44
5	F5	46

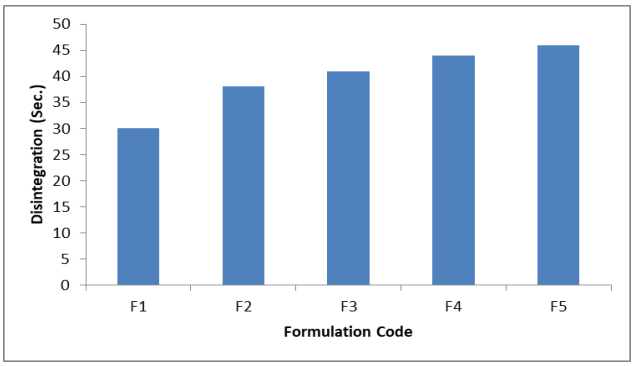

Figure 4: Determination of disintegration time of different formulations of CPM fast dissolving films (F1-F5).

DRUG CONTENT UNIFORMITY

Percentage of drug content for different formulations was calculated and the results were shown in the table 9.

Table 9: Determination of drug content uniformity for different formulations of CPM mouth dissolving films (F1-F5).

S.No.	FORMULATION	DRUG CONTENT (%)
1	F1	97
2	F2	96.9
3	F3	97.2
4	F4	97.23
5	F5	97.45

Percentage of drug content of F1-F5 was found to be 97-97.45% and F1 was considered as best formulation compared to the other formulation. The formulations F1 showed percentage drug content 97%. From the results obtained from the above formulations. The drug content of films should be complies with the limit as 85-110% as per IP specifications (IP 2007).

***In-vitro* diffusion studies**

Drug release studies of all formulated batches were studied and it was observed that F1 batch releases > 80 %drug at the end of 14 min (table 10 & figure 5).

Table10: Drug release profile of all formulated batches.

Time (minutes)	Cumulative percentage release of CPM containing fast dissolving film				
	F1	F2	F3	F4	F5
0	0	0	0	0	0
2	24	22	20	18	18
4	39	37	36	35	34
6	44	42	39	35	33
8	50	45	41	37	35
10	64	59	55	51	49
12	77	72	68	64	61
14	82	77	73	69	66
16	87	82	78	70	67

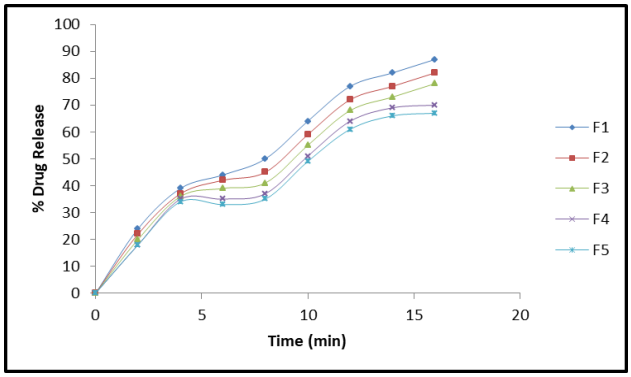

Figure 5: Drug release study of all formulations containing DRC of CPM.

CONCLUSION

Mouth dissolving films of taste masked DRC of CPM were prepared using Xanthan gum and and PEG as a plasticizer. All the formulated batches of films were found to disintegrate within 60 sec. Among all formulated batches the prepared formulations F1 showed minimum disintegration time of 30 seconds. Mouth dissolving films were prepared successfully by the use of Taste masked complex of CPM and it can be used to treat geriatric, pediatric bedridden and non-cooperative patients.

REFERENCES

1. Roy, G.M.The applications and future implications of bitterness reduction and inhibition in food products. *Crit. Rev. Food Sci. Nutr*, 1990; 29(2): 59–71.
2. Roy, G. Bitterness: reduction and inhibition. *Trends Food Sci. Tech*. 1992; 3: 85–91.
3. Avinash MR, Devi KV, Asha AN. "A novel technique for the preparation of mouth dissolving tablets of Domperidone". *Ind Drugs*, 2003; 40(9): 544-546.
4. Patel DM, Patel NM, Shah RR, Gogan PD, Patel AI. "Studies in formulations of oro-dispersible tablets of Rofecoxib". *Ind J Pharm Sci*, 2004; 66(9): 621-625.
5. Sharma S Lewis S. "Taste Masking Technologies: A Review". *Int J of Pharm and Pharm Sci*., 2010; 2(1): 6-13.
6. Guyton C. Hall J E. "The Chemical Senses- Taste and Smell". Textbook of Medical Physiology. Guyton and Hall Editors.11th Ed. Hong Kong; W.B. Saunders Company, 2007.
7. Gruetter CA, Lemke SM, Anestis DK, Szarek JL, Valentovic MA. Potentiation of 5-hydroxytryptamine-induced contraction in rat aorta by Chlorpheniramine, Citalopram and Fluoxetine. Eur J of Pharmacology, 2013; 217: 109–118.
8. Nair AB, Kumria R, Harsha S, Mahesh A, Bandar E, Alhaider IA. In vitro techniques to evaluate buccal films. J Controll Release, 2013; 116: 10-21.
9. Sharma V, Chopra H. "Role Of Taste And Taste Masking Of Bitter Drugs In Pharmaceutical Industries- An Overview" Published In *International Journal Of Pharmaceutical Professional Science*, 2010; 2(4): 14 -18.
10. Sharma V, Singh L. Formulation Variable Study And Optimization Of Taste Masked Mouth Dissolving Tablets Using Design Of Experiment. *Drug Development and Therapeutics*, 2015; 6(1).
11. Sumedha Bansal, Mayank Bansal1 and Gopal Garg, formulation and evaluation of fast dissolving film of an antihypertensive drug,international journal of pharmaceutical, chemical and biological sciences, 2011;3(4): 1097-1108.
12. Vishwkarma DK, Tripathi AK, Yogesh P, Maddheshiyab B. Review article on mouth dissolving film. J Glob Pharm Technol, 2001; 3: 1–8.
13. Francesco C, Irma EC, Paola M, Francesca S and Luisa M: Fast dissolving films made of maltodextrins. European Journal of Pharmaceutics and Biopharmaceutics 2008; 70(3): 895-900.