Original Research Article

Optimization and evaluation of Favipiravir Orodispersible films as a promising therapeutic approach for COVID-19

ABSTRACT

Introduction: Oro Dispersible Films (ODF) is a thin strip that is mostly transparent, biodegradable and it has hydrophilic polymers that disintegrate and dissolves immediately when getting contact with saliva.

Aim: To formulate Orodispersible films of favipiravir and to study the effect of different superdisintegrants on various film properties.

Methods: The method used to prepare the film is the solvent casting method. In this method, the solution is prepared using polymer, drug, and superdisintegrants. This solution is casted on a film-forming apparatus using a spreader an instrument to obtain a thin film.

Results: The prepared oral films weights ranging from 148mg to 237mg based on the superdisintegrant concentration. The pH of the prepared films didn't vary significantly and percent moisture absorption doesn't have significant variation. However, the texture varied from smooth to rough and transparent to translucent. Disintegration time is varying from 28 to 42 seconds. The optimum batch formulation gave 98% of drug release.

Keywords: Favipiravir, Oral films, Superdisintegrants

Introduction:

From past decades patient compliance is being improved from one formulation to another formulations. The main aim here is to improve patient compliance by not effecting the drug delivery to the body. For this approach,Oro-dispersible films which are very thin, can be taken without water just by placing them on tongue. Also, in many cases taste of the drug can be masked by taste-masking agents, just by incorporating them into oral films. Orodispersible films are commercially available since 1970s itself[(1)].

ODF is a thin strip that is mostly transparent, biodegradable and it has hydrophilic polymers that disintegrate and dissolves immediately when getting contact with saliva[(2)]. Most of these films are useful for drug delivery in pediatric and geriatric patients. Using a conventional dosage form decreased patient compliance, so Oro Dispersible tablets are first developed. Still, these tablets may disintegrate faster but there come several disadvantages such as less hardness, brittleness, and the risk of choking [(3)].To get films, commonly used polymers are Hydroxypropyl cellulose (HPC), and Hydroxypropyl Methyl Cellulose (HPMC) using solvent casting technique[(4)]. This can be achieved by using Film Former apparatus (VJ INSTRUMENTS^{TM}). The obtained films are evaluated based on various, evaluation parameters such as thickness of the film, Tensile strength, disintegrating time, folding endurance, moisture uptake analysis, *In-vitro* dissolution studies. The obtained or prepared film should pass all the evaluation parameters.

Favipiravir is a modified pyrazine analog discovered by Toyama Chemical Co., Japan. It was initially used against influenza. Favipiravir inhibits RNA-dependent RNA polymerase (RdRp) of RNAviruses[5].Favipiravir is contraindicated in pregnancy as it is having potential embryotoxicity. Favipiravir is also excreted in human breast milk; hence it is also contraindicated in childbearing women[6]. The structure of Favipiravir is given in Figure 1.

Comment [MOU1]: Absent: structure

COVID-19 which is originated in Wuhan, China in 2019 and was declared a pandemic by WHO on March 12th, 2020[7].The virus which is causing influenza in patients was identified to be Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-Cov-2). The constant research is going on repurposing of drugs such as hydroxychloroquine, remdesivir, lopinavir, ritonavir, and some drugs previously existing against COVID-19 treatment. The previously existing drug Favipiravir is showing effectiveness in SARS-CoV and MERS (Middle East Respiratory Syndrome) which are having similarity in the Genome sequence of SARS-CoV-2. Hence, favipiravir is studied for its effectiveness in the treatment of SARS-CoV-2[8]. The dosage for adults is varying from 600-800 mg, whereas in children 100 mg to 200 mg is given. In present research, each of the films are loaded with 100 mg of drug. So, two films can be given as a single dose or one film based on severity of the disease. The present study involves the study of drug release from oral film, and compatibility of drug with excipients involved in the preparation of oral films. These films help in the faster release of drug when compared to conventional tablets.

Experimental Part:

Materials and Methods:

Favipiravir API was received as a gift sample from Biophore Pvt Ltd, Hyderabad. Hydroxy Propyl Methyl Cellulose E50 LV (LobaChemiePvt.Ltd, Mumbai) is used as a film former. Sodium Starch Glycollate (LobaChemiePvt Ltd, Mumbai), Microcrystalline cellulose (LobaChemie Pvt Ltd, Mumbai), Cross Povidone (FMC Biopolymer) were used as superdisintegrants. Propylene glycol (Qualigens fine chemicals) was used as a plasticizer. Aspartame as a sweetener. Distilled water as a solvent.

Various equipment used in the preparation of oral films are Electronic Balance, Ax 200 (Shimadzu corporation), Magnetic stirrer 5MLH DX (Remi Japan), Film Former (Vj instruments, Mumbai), pH Meter (Elico Ltd Hyderabad), Glassware (Borosil), Dissolution Apparatus (Lab India Disso 8000), Weighing balance (SHIMADZU ELB 300).

Comment [MOU2]: what is the idea of mentioning the equipments?

Method used:

Oral film was prepared by the solvent evaporation method. In a beaker distilled water of the required amount is taken. Using a magnetic bead, the water was stirred, to this HPMC E50 LV (polymer) of required quantity was added. Then the solution was mixed with drug solution. To this mixture different super disintegrants as mentioned in formulation F1 – F9 (Table 1) were added based on formulation requirements. After complete mixing to this solution, PEG is added as a plasticizer. Aspartame is added as a sweetener and mixed using Magnetic Stirrer (5 MLH Remi). The obtained solution was kept aside for about 15 minutes

to make it bubble-free and spread using a spreader on a film former apparatus. The temperature was set to 40° C. After drying we get a thin layer film which is then removed and evaluate

Table:1 All formulations of Favipiravir oral films

S. No	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
1	Favipiravir	200	200	200	200	200	200	200	200	200	200	200	200
2	HPMC E50 (%W/V)	5	5	5	5	5	5	5	5	5	5	5	5
3	Sodium Starch Glycollate (%w/v)	2	4	6	-	-	-	-	-	-	2	-	2
4	Microcrystalline cellulose (%w/v)	-	-	-	2	3	4	-	-	-	-	2	2
5	Cross povidone (%w/v)	-	-	-	-	-	-	1	2	3	1	1	-
6	Propylene glycol (ml)	2	2	2	2	2	2	2	2	2	2	2	2
7	Aspartane mg	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
8	Water (ml)	10	10	10	10	10	10	10	10	10	10	10	10

Evaluation:

Preparation of standard graph of Favipiravir:

10mg of favipiravir was dissolved in 10ml of water using a cyclo mixer. This solution is referred to as a standard solution. From the standard solution make 10µ/ml stock solution was made and measured for the maximum wavelength obtained using UV-VIS spectrophotometer. The obtained wavelength is selected as λmax. The obtained spectrum is 235nm. Different stock solutions of 3, 6, 9, 12, and 15µg/ml were prepared and observed for their linearity. The standard curve was plotted.

Thickness: 10 films were selected randomly and thickness was measured using screw gauge (20×1/100). The four corners of each film and the center of the film thickness is measured and average thickness of each films is calculated(9).

Comment [MOU3]: super index

Physical appearance and texture analysis: By visually inspecting the film some parameters were measured by feel and touching the film(10).

Weight Variation:10 Films were randomly selected for every formulation made. The average weights of films were calculated (11).

Content uniformity: The formulated films were cut into required size (3×4 cm^2) and taken in a 100 ml volumetric flask containing 6.8 pH phosphate buffer (12). The solution was sonicated for 20 minutes and an aliquot of solution was filtered through a 0.22-micron filter and UV absorbance was measured at 235 nm against blank. Using a standard graph, the concentration of solution was measured.

Folding endurance (13)**:** Folding endurance of films are measured to know the withstanding capability of films at the time of packing. The procedure involved is repeatedly folding a small strip of the film till it was broken. The number of times the film folds without any breaks gives the folding endurance value of the film.

Surface pH of the film: The surface pH may be measured to avoid possible irritation to the mouth by acidic or basic nature of film. The surface pH of oral was measured using pH meter. Film was taken along with 1 ml of distilled water. Kept at room temperature for 1 hour(14).

Percent Moisture Loss, absorption(15):3 films of different formulations are taken and weighed and placed in desiccator containing calcium carbonate for 72 h. After 72 h the patched are weighed and taken as final weight. The moisture loss was calculated using the formula given below.

$$percent\ moisture\ loss = \frac{initial\ weight - final\ weight}{initial\ weight} \times 100$$

Moisture uptake of oral film was determined by exposing the film at 75% relative humidity for 72 h and the Percent moisture uptake was calculated using below formula

$$percent\ moisture\ uptake = \frac{final\ weight - initial\ weight}{final\ weight} \times 100$$

***In vitro* disintegration:** The film was cut into 3×4 cm^2 as a unit dose. This film was placed on a petri dish containing 10 ml of distilled water(10). The time required for a film to disintegrate is noted. The results are varying from 28 to 43 seconds depends upon the concentration of polymer used, the detailed result is given in (table 3)

***In vitro* dissolution:** Drug release from the prepared oral films were studied using dissolution test apparatus. The desired formulations were placed in the vessels containing 900 ml of 6.8 pH Phosphate buffer. USP type 1 basket type apparatus was used. Samples were collected at regular intervals for 15 minutes. The percent (%) of drug released or dissolved was calculated. 3 films of every formulation were taken individually and mean is calculated.

Results and Discussion:

Drug Excepient Compatibility(16):

Analysis of pure drug and excipients physical mixture was done using FTIR pellet press method using Potassium Bromide. And obtained graphs were observed for their spectra wavelengths.

Drug-excipient compatibility ~~compatibility~~ studies sing carried out using FTIR. The figure 1 explains about pure drug spectrum. Pure drug combined with polymer (HPMC E 50) from the graph (Figure 2) it shows they are compatible. The pure drug is mixed with the 3 different super disintegrants (Sodium starch Glycollate, Micro Crystalline Cellulose and Cross Povidone) separately, shows good compatibility to each other (Figure 2,3,4,5). Shows that all the excipients are compatible with pure drug.

Comment [MOU4]:

Table 2

Comment [MOU5]: What do you mean by this?

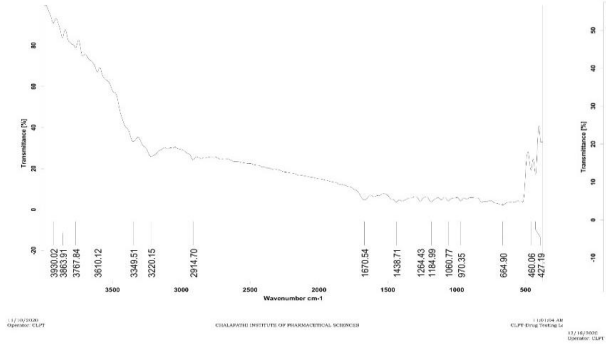


Fig. 1. FTIR of Pure Drug Favipiravir

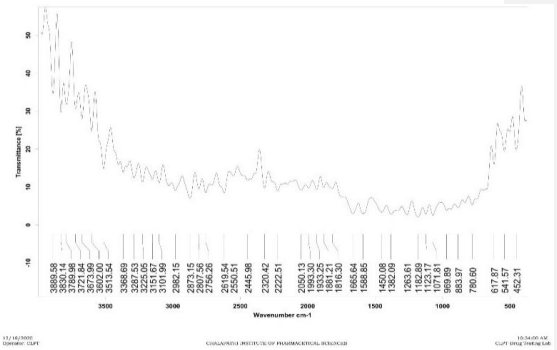


Fig. 2. FTIR of Pure Drug and HPMC E50

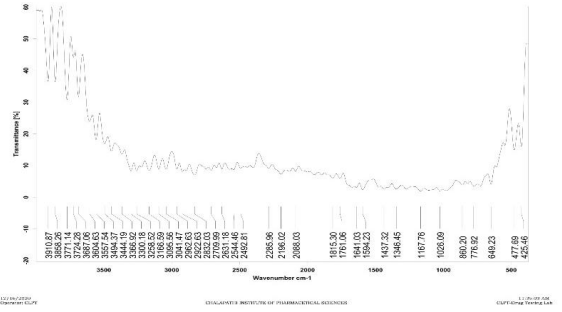


Fig 3 FTIR of Pure Drug and SSG

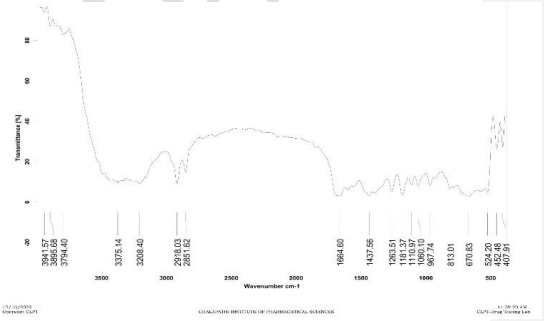


FIG 4 FTIR of Pure drug and MCC

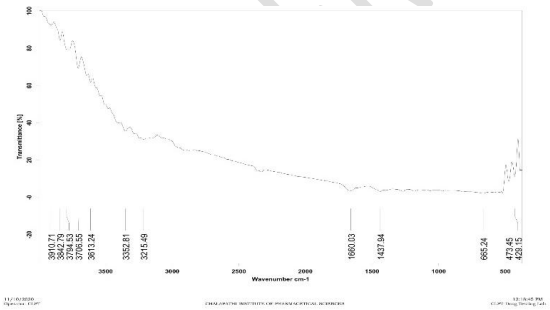


FIG 5 FTIR of Pure drug and CPV

Standard Calibration graph: From the standard spectrum (Figure 6) we can observe that the maximum wavelength is 235nm, so all the obtained stock solutions were scanned using UV-Spectrophotometer to get standard calibration graph (Graph 1)

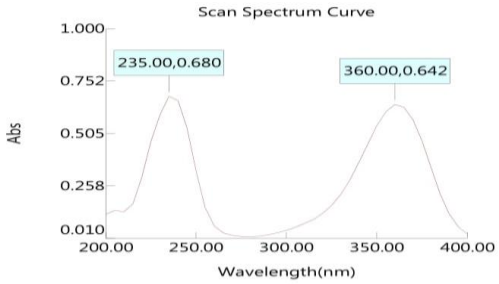
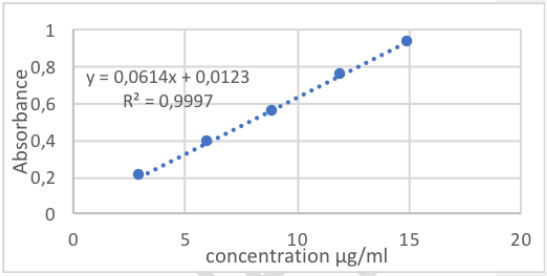


Fig 6 UV spectrum Standard graph



Graph 1 Standard calibration Graph of Favipiravir

Surface pH: All the prepared films have pH ranging from 6.6-6.8 which is similar to neutral and hence they are in acceptance criteria. The (table 2) shows detailed information about pH of different formulations.

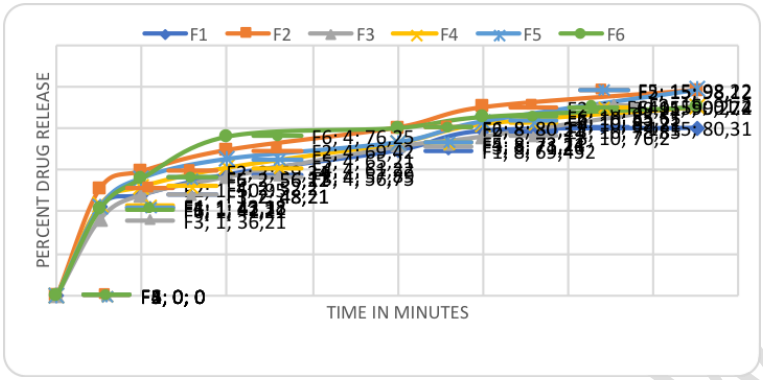
Formulation code	pH	Result
F1	6.81	Pass
F2	6.62	Pass
F3	6.83	Pass
F4	6.67	Pass
F5	6.62	Pass
F6	6.84	Pass
F7	6.65	Pass
F8	6.64	Pass
F9	6.62	Pass
F10	6.80	Pass
F11	6.71	Pass
F12	6.78	Pass

Table 2 pH of different formulations

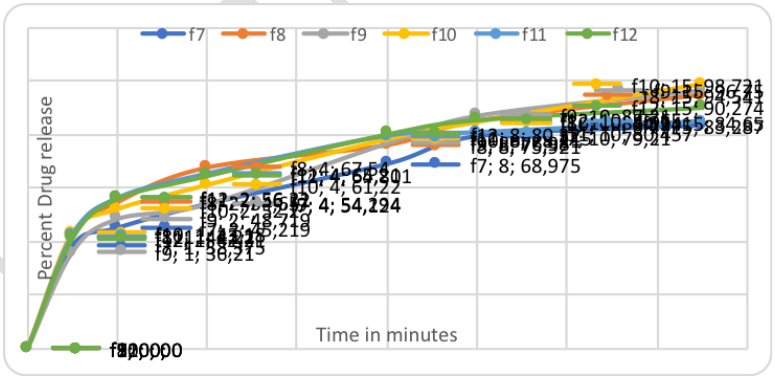
In vitro **Dissolution studies:** The graphs 2 and 3 gives a detailed information about drug release from various formulations F1-F12.

Table 3 Various evaluation tests of films

Formulation code	Thickness (mm)	Physical appearance	Texture	Content Uniformity (mg)	Weight variation	Percent Moisture Loss (%)	Percent Moisture absorption	Folding endurance	Disintegration time in seconds
F1	0.136±0.05	Transparent	Smooth	98.8±0.36	148.3±0.26	4.46±0.11	6.14±0.03	55±1	35±0.57
F2	0.172±0.06	Transparent	Smooth	100.13±0.9	199.9±0.7	4.6±0.1	6.24±0.02	98±4.72	30±1
F3	0.153±0.03	Transparent	Smooth	99.36±0.15	237.83±1.16	4.79±0.09	6.75±0.05	99±3.15	39±1.5
F4	0.198±0.025	Transparent	Smooth	98.3±0.26	151.23±0.35	4.98±0.1	6.67±0.04	56±2.21	34±0.46
F5	0.265±0.01	Translucent	Rough	100.73±0.72	181.42±0.57	5.26±0.075	6.59±0.08	62±2.41	35±1
F6	0.284±0.014	Translucent	Rough	99.4±0.3	200.3±0.242	5.33±0.17	6.47±0.05	67±2.36	42±0.35
F7	0.178±0.048	Transparent	Smooth	99.1±0.17	121.08±0.24	4.52±0.045	6.77±0.03	56±4.58	33±1
F8	0.284±0.029	Transparent	Smooth	99.26±0.2	151.096±0.46	4.7±0.06	6.67±0.03	65±6.21	34±1.56
F9	0.271±0.03	Transparent	Smooth	99.16±0.11	181.02±0.75	4.8±0.05	6.43±0.04	96±1	32±1.21
F10	0.231±0.05	Transparent	Smooth	98.3±0.26	188.06±0.77	4.69±0.08	7.67±0.04	101±1.57	28±1.37
F11	0.367±0.01	Translucent	Rough	100.8±0.6	180.87±0.56	4.75±0.03	7.19±0.02	98±0.57	37±1
F12	0.398±0.016	Translucent	Rough	99.38±0.36	200.44±0.49	4.81±0.02	7.29±0.07	99±0.46	33±0.57



Graph 2 *In vitro* data of Formulations



Graph 3 *In vitro* data of Formulations F7-F12

Conclusion:

From various formulations it is estimated that, as the concentration of super disintegrants increases the thickness is also increasing as we seen in formulas F3, F6, F9. The formulations involved with Micro Crystalline Cellulose gave rough surface on the film however F4 shows at low concentration giving smooth surface texture. Of all the formulations it is identifies that formulations F2 and F10 are found to be good when compared to other formulations.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

References:

1. Takehisa Hanawa, Atsushi Watanabe, Takanori Tsuchiya, Rieko Ikoma, Masato Hidaka MS. New Oral Dosage Form for Elderly Patients: Preparation and Characterization of Silk Fibrion Gel. Chem Pharm Bull. 1995;43(2):284–8.
2. Dixit RP, Puthli SP. Oral strip technology: Overview and future potential [Internet]. Vol. 139, Journal of Controlled Release. Elsevier B.V.; 2009. p. 94–107. Available from: http://dx.doi.org/10.1016/j.jconrel.2009.06.014
3. Bhyan B, Jangra S, Kaur M, Singh H. Orally fast dissolving films: Innovations in formulation and technology. Vol. 9, International Journal of Pharmaceutical Sciences Review and Research. 2011. p. 50–7.
4. Siddiqui MDN, Garg G, Sharma PK. A Short Review on " A Novel Approach in Oral Fast Dissolving Drug Delivery System and Their Patents " Conventional oral Modified release Fast action oral solid. Int J Pharm Sci Rev Res. 2011;5(6):291–303.
5. Furuta Y, Komeno T, Nakamura T. Favipiravir (T-705), a broad spectrum inhibitor of viral RNA polymerase [Internet]. Vol. 93, Proceedings of the Japan Academy Series B: Physical and Biological Sciences. 2017. p. 449–63. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5713175/pdf/pjab-93-449
6. Nagata T, Lefor AK, Hasegawa M, Ishii M. Favipiravir: A New Medication for the Ebola Virus Disease Pandemic. Disaster Med Public Health Prep. 2015;9(1):79–81.
7. Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, et al. Early Transmission Dynamics

in Wuhan, China, of Novel Coronavirus–Infected Pneumonia. N Engl J Med. 2020;382(13):1199–207.

8. Kaur RJ, Charan J, Dutta S, Sharma P, Bhardwaj P, Sharma P, et al. Favipiravir use in COVID-19: Analysis of suspected adverse drug events reported in the WHO database. Infect Drug Resist. 2020;13:4427–38.

9. Kulkarini Parthasarathi Keshavarao, Dixit Mudit GK. FORMULATION AND EVALUATION OF MOUTH DISSOLVING FILM CONTAINING ROFECOXIB. Int J Pharm. 2011;2(3):273–8.

10. Kanth NP, Prasad G, Kumar BV. Oral Dissolving Films of Chlorpheniramine Maleate. Int J Pharm Sci Res 2014;5(5):1859–73. Available from: http://www.wjpr.net/download/article/1404198266.pdf

11. Reyad-ul-Ferdous, Shahjahan DS. EFFECTIVE DEVELOPMENT AND EVALUATION OF ORAL THIN FILM OF ETORICOXIB. World J Pharm Res. 2015;4(9):257–72.

12. Alam M, Tasneem F, Pathan MSI. Formulation and Evaluation of Swellable Oral Thin Film of Metoclopramide Hydrochloride. Bangladesh Pharm J. 2015;17(1):102–12.

13. Nishimura M, Matsuura K, Tsukioka T, Yamashita H, Inagaki N, Sugiyama T, et al. In vitro and in vivo characteristics of prochlorperazine oral disintegrating film. Int J Pharm. 2009;368(1–2):98–102.

14. Raza SN, Kar AH, Wani TU, Khan NA. Formulation and evaluation of mouth dissolving films of losartan potassium using 32 Factorial design. Int J Pharm Sci Res [Internet]. 2019;10(3):1402–11. Available from: http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L626825396%0Ahttp://dx.doi.org/10.13040/IJPSR.0975-8232.10(3).1402-11

15. Reddy PS, Ramana Murthy K V. Formulation and evaluation of oral fast dissolving films of poorly soluble drug ezetimibe using transcutol Hp. Indian J Pharm Educ Res. 2018;52(3):398–407.

16. Sreekanth M, Gulshan M, Gupta EM, Rama Rao N. Design and evaluation of ORO - Flash release films of amlodipine besylate. Int J Pharm Sci Res [Internet]. 2014;5(6):2428–35. Available from: http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L373204609%0Ahttp://dx.doi.org/10.13040/IJPSR.0975-8232.5(6).2428-35