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Design and Development of Biodegradable Patch in Capsule containing model drug for treatment of Ulcers

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ABSTRACT:
Oral dosage is most prominent route for both conventional and novel drug delivery systems. Different kinds of formulations were targeted via oral route for different types of diseases. Thus improve the pharmacokinetic parameters of medications; some of the novel formulations with sustained release and control release were formulated. But there is still a big challenge to show gastric residence time for formulations that having short half-life. So many approaches have been adopted by researchers as well as by pharmaceutical industries to improve the gastric residence time for formulations. Due to certain disadvantages of such gastro- retentive drug delivery formulations, Patch in capsule drug delivery is the best option to improve the pharmacokinetic parameters as well as the time of gastric residence of such formulations. Patch in capsule is a novel technique designed to increase the duration of gastric residence of drugs and enhance the pharmacokinetic properties of different drugs. Patch in capsule is a formulation of the control release following kinetics in zero order.Patch in Capsule is suitable for drugs having narrow absorption window (which are absorbed by saturable transport). It is anticipated that the Patch in Capsule will provide a valuable pharmaceutical solution to enhance therapy with narrow absorption window drugs.After evaluation it was observed that the patch shows equal distribution of drug in a prepared patch and prepared patch in capsule of amoxicillin shows better release rate than a marketed formulation of amoxicillin. The effect of release rate is that a marketed formulation shows almost 90% above in 1 hour but Patch in capsule shows extend rate release 70% in 2 hours and was still proceding.

Keywords: Oral dosage, control release, rate release, gastro retentive, zero order, gastro-retentive, novel formulation, patch in capsule.

I. INTRODUCTION

A controlled dosage form means a dosage form, which continuously releases a or more medications, either systemically or locally, into specific target organ for a fixed period of time, in a predetermined pattern(Hwang et al., 2019). Further focus has been given to the development of oral controlled drug delivery systems (GRDDS) because of versatility in the design of dosage shapes. The main challenges facing oral drug delivery systems are delivering a medication at the appropriate location at a therapeutically effective rate, modulating GI transit time and reducing first-pass elimination(Zhao et al., 2014). Maintenance of the maximum and active medication dosage for a long period, with lower dose levels and secondary effects is enhanced through the control release form.Small dose quantities are administered as in case of control release drug delivery through particular routes to minimize the adverse effects and maximize the pharmacokinetic parameters as well as pharmacodynamics parameters. It also shows better recovery for patient's health in short period of time as it decreases the variability in biopharmaceutics(Gupta et al., 2018). The formulation those show immediate drug release got some limitations like site targeting, maintenance of dosing frequency and especially control release. Ideally treatment for longer period of time, the formulations should release rate should be optimum.

To encounter the barriers determined by gastrointestinal tract like reduction in frequent dose requirement, incomplete drug release and dose effectiveness, conventional drug delivery system is not applicable (Liang et al., 2019). Gastro-retention drug delivery system has advantages for formulations by increasing gastric residence time in the stomach for

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longer period, optimizes the absorption of dosage forms to prove therapeutic efficacy and relevant route to stomach for target drug delivery. It enhances the property of formulations by releasing the medicament in a control manner for longer period of time by releasing the drug continuously at desired site of absorption along with desired rate(Misra & Singh, 2018).

From long time the developments have been done by scientists and researchers for drug delivery systems to overcome the limitations such as less gastric residence time, uncertain gastric emptying time and absorption through several physiological barriers(Anselmo & Mitragotri, 2014). They formulated oral rate control release drug delivery to enhance the limitations of drug delivery systems.The drugs having gastric residence time, an absorption in the upper gastro-intestinal tract is limited as in case of conventional drug delivery systems (tablets, capsules and granules).Such drugs ideally are delivered from stomach to site of action (to provide localize effects) in control manner or slowly released. Demonstration of drugs has been categorized in order to show optimum absorption is dependent on gastric retention time of dosage form. Thus, drug designing is done for drugs so that they show gastric retention time and better absorption.Drugs with absorption in the bottom part of gastrointestinal tract, volatile and poorly soluble in alkaline pH, limited half-life and locally active in upper GI tract to remove Helicobacter Pylori (H. pylori) are essential for gastric retention drug delivery(Narendra et al., 2006).Modeling strategy for active controlled GRDDS release systems has been used for many applications including super porous hydrogels, mucoadhesive, raft-forming, magnetic and ion exchange systems, expandable, low and high density. The consistency of gastro-retention dosage is influenced by various factors associated with the formulation, such as polymer types (Nonionic, cationic and anionic polymers), dose shaped polymer structure, viscosity level, molecular polymer weight, and drug solubility. The physical chemical nature of the excipients in particular GRDDS plays an important role(Prajapati et al., 2011).

II. NOVEL APPROACHES FOR DRUG DELIVERY

Forms of gastro-retentive doses (GRDFs) are designed for long-term retention in the stomach and release of active ingredients, thus allowing the drug to be input onto the upper part of the gastrointestinal (GI), sustaining and prolonging its input.This technology has generated tremendous interest over the last few decades due to its potential application to improve the oral delivery of certain important drugs, for which prolonged persistence in the upper GI tract will greatly enhance their oral bioavailability and/or therapeutic outcome.

Patch in capsule plays a role for novel gastro retentive drug formulation. Gastric retention for such formulation can be achieved by maintaining its size, shape, mechanical and physical properties. This formulation consists biodegradable multilayer polymer film that is folded and designed in such a way that it gets fixed into a standard capsule size. Generally, the Patch in Capsule contains control release layer (inner layer), layer containing drug, unfolding layer (outer layer), and immediate release rate layer for different drug release profiles or combined fixed doses. Upon reaching the stomach, the capsule dissolves in such a manner so that the structure unfolds and will retain in the stomach for longer period of time. Patch in stomach will release the medicaments in controlled manner from stomach to the absorption site (upper gastro-intestinal tract). After Release of drug patch will move towards the small intestine to get degraded, as it contains the enteric coated material. Being soluble in intestine pH, the Patch will get degraded easily and will be eliminated out from the body. Due to this formulation (Patch in Capsule) there will be increase in pharmacokinetic and gastric retention time of formulation without recommendation of any special meal.

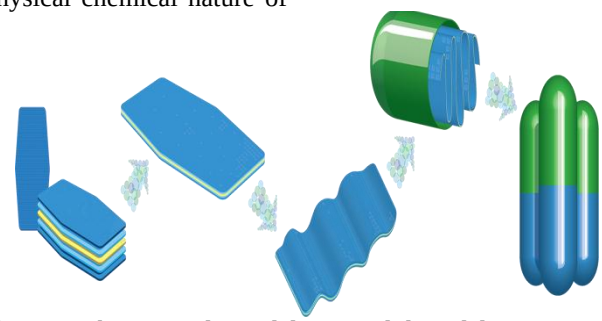

Fig 1: Patch in capsule model as novel drug delivery systems

III. MATERIAL AND METHODS

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Preparation of patch:

Formulation

Material	Ratio	solvent
PVP K-30: PVA	1:1 and 1:2	Water
ETHYL CELLOLOSE: PVA	1:1 and 1:2	Water

Table A. formula for preparation of patch.

Solvent casting method:

Model for patch in capsule is prepared by solvent casting method. In this method specified petri dish is selected with proper size. Accurately polymers are weighed and dissolved in water (10mL) and methanol (10mL). Solution is kept aside so it gives a clearsolution.Drug (Amoxicillin) is added to above solution and mixed continuously till the clear solution is formed. Polyethylene glycol 400 (30% w/w of total polymer) is used as plasticizer and propylene glycol (15% w/w of total polymer) is used as permeation enhancer. The casting is done on petri dish for resulted solution and before casting petri plate is lubricated with glycerine. The solution is dried at room temperature for 24 hours. Funnel is placed over the petri plate so to limit the fast evaporation of the solvent. For further studies patch is taken from petri plate after 24 hours and stored in a desiccator.

Characterization of formulation.

1. Folding endurance: We had cut the patch in the dimension of (2×2)cm. Patch was folded and opened repeatedly till the Patch got broken. The number at which Patch got broken was determined and marked as the folding endurance. Folding endurance = No. of Repeated folding at which Patch Breaking Occur.

2. Surface pH: The patch was placed in a beaker containing water for 1 hour to get swell up. The pH electrode was calibrated and then the electrode was contacted with the surface of patch for 1 min. Calibration of the pH meter was done by the buffer tablets.

3. Thickness: Patch with a proper dimension of 2 * 2 cm was taken and the Thickness of Patch was determined by Vernier Caliper. Vernier caliper was exposed for measurement at three different sites of the Patch. Finally, the average was calculated.

4. Drug content uniformity: Patch (2×2 cm) was cut into four equal halves. Each part was dissolved in 0.1N HCl and the drug concentration present in each half was observed through UV-spectroscopy at λmax = 325nm

5. Invitro Release studies: Dissolution of Patch in Capsule formulation: Capsule shell (Gelatin base) with size 000 was taken and the prepared Patch of Amoxicillin was folded and fitted inside the capsule shell. 0.8 ml of concentrated HCl was dissolved in 1000 ml of distilled water (0.1N HCl). The temperature was maintained at 37°C and the beaker was filled with 900 ml of 0.1 N HCl. Amoxicillin capsule was placed in beaker containing 0.1N HCL and the paddle was set at 100 rpm. Initially the 5 ml was taken and 5 ml of 0.1N HCl was added to maintain sink condition. Continuous process of taking 5 ml and adding 5 ml buffer to it, after the interval of 5 min. The samples were taken for reading at UV at a λmax = 325nm. Graph was plotted between concentration and time to get rate release.

IV. RESULT AND DISCUSSION

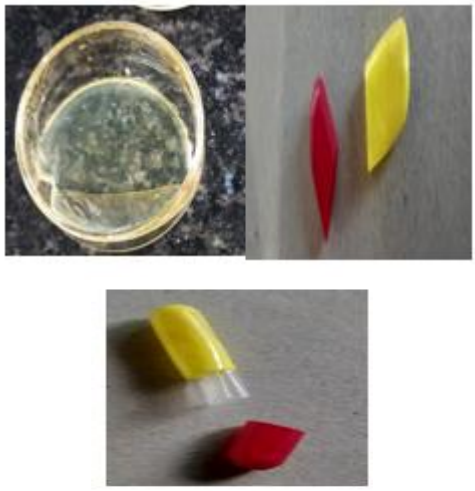

Figure 2:-Prepared Patch in Capsule formulation.

FTIR of chemicals

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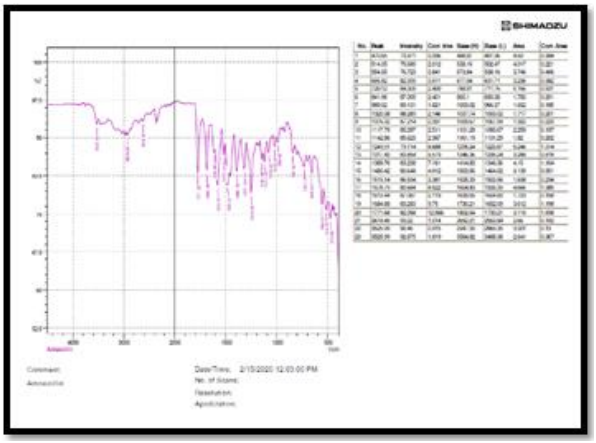


Figure 3:-FTIR of Amoxicillin.

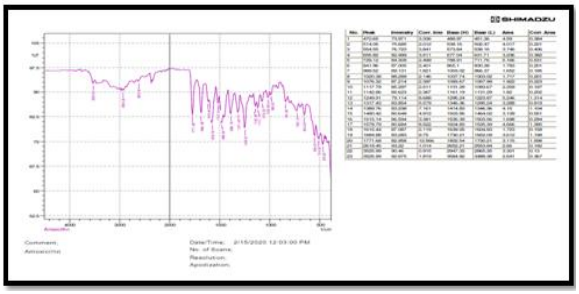


Figure 4:-FTIR of Ethyl cellulose.

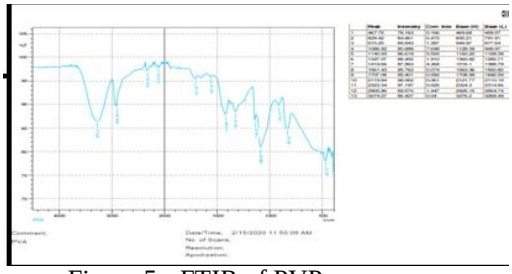
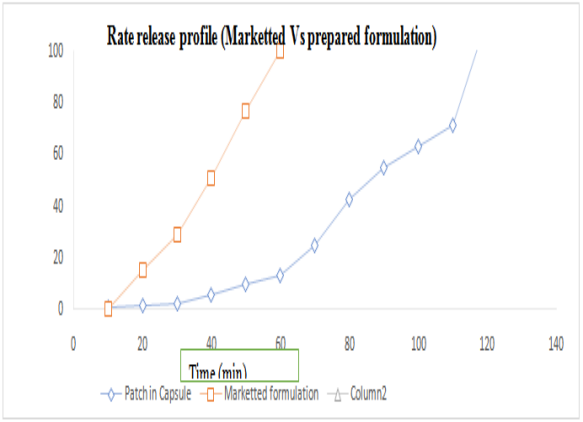


Figure 5:- FTIR of PVP.

Properties	Inference
Color	Colorless
Odor	Odorless
Taste	Tasteless

Table 1. Organoleptic properties of patch



S.No	Folding Endurance	Surface pH	Content uniformity	Mean Thickness (mm) ±SD
F1	198 ± 5	6.08 ± 0.005	2.41 ± 0.017	0.213 ± 0.005
F2	192 ± 4	6.12 ± 0.023	2.47 ± 0.016	0.225 ± 0.003
F3	196 ± 5	6.18 ± 0.001	2.48 ± 0.052	0.233 ± 0.007
F4	201 ± 2	6.09 ± 0.002	2.48 ± 0.062	0.2480.006

Table 2. Physical properties of amoxicillin patch.

S.No	Conc. (mcg/ml)	Absorbance			Mean ± SD
		Trial 1	Trial 2	Trial 3	
1	0	0.000	0.000	0.000	0.000±0.000
2	10	0.050	0.043	0.046	0.046±0.004
3	20	0.097	0.095	0.098	0.097±0.002
4	30	0.143	0.144	0.146	0.144±0.002
5	40	0.185	0.188	0.187	0.187±0.002
6	50	0.240	0.237	0.237	0.238±0.002

Table 3. UV readings of Amoxicillin.

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Time	Absorbance	Concentration	Conc. * dilution Factor	Conc. In 900ml	Cummulative Conc.	Conc. in mg	% drug release
10	0.002	0.425531915	4.255319149	3829.787234	3839.78	3.83978	0.7678
20	0.0031	0.659574468	6.595744681	5936.170213	9765.957447	9.76595745	1.953191489
30	0.0039	0.829787234	8.29787234	7468.085106	13404.25532	13.4042553	2.680851064
40	0.012	2.553191489	25.53191489	22978.7234	30446.80851	30.4468085	6.089361702
50	0.0145	3.085106383	30.85106383	27765.95745	50744.68085	50.7446809	10.14893617
60	0.0202	4.29787234	42.9787234	38680.85106	66446.80851	66.4468085	13.2893617
70	0.0456	9.70212766	97.0212766	87319.14894	126000	126	25.2
80	0.0652	13.87234043	138.7234043	124851.0638	212170.2128	212.170213	42.43404255
90	0.078	16.59574468	165.9574468	149361.7021	274212.766	274.212766	54.84255319
100	0.088	18.72340426	187.2340426	168510.6383	317872.3404	317.87234	63.57446809
110	0.098	20.85106383	208.5106383	187659.5745	356170.2128	356.170213	71.23404255
120	0.198	42.12765957	421.2765957	379148.9362	566808.5106	566.808511	113.3617021

Table 4. UV reading of Patch in Capsule at different time intervals.

Patch in Capsule is suitable for drugs having narrow absorption window (which are absorbed by saturable transport). It is anticipated that the Patch in Capsule will provide a valuable pharmaceutical solution to enhance therapy with narrow absorption window drugs. The λmax of amoxicillin was found to be 325 nm (range 200-400 nm) in 0.1 N HCl and stimulated gastric buffer pH-1.2. In pre-formulation studies, it shows better folding endurance of 201± 4, surface pH-6.8±0.5 and a patch thickness with 0.202± 0.03 mm. Standard plot of amoxicillin was done by plotting a graph between absorbance and concentration. The concentration of 10 mcg, 20 mcg,30 mcg, 40 mcg, 5o mcg,60 mcg was made by the dilution method from the stock source of amoxicillin containing 1mg/ml concentration. With the help of blank (0.1 N HCl) the UV-spectroscopy to find out drug content uniformity was done. In drug content uniformity standard patch was cut down into equal halves and dissolved in 0.1 N HCl for 24 hours. After 24 hours the content was exposed to UV-Spectroscopy at a range of 200-400 nm to find out the drug content uniformity. After evaluation it was observed that the patch shows equal distribution of drug in a prepared Patch. Rate and extend release process of Patch in Capsule was done through dissolution process consisting dissolution apparatus (basket and USP 2 paddle). Initially the basket was filled with 900 ml of buffer and temperature was maintained 37±0.5 degree Celsius. Throughout the process sink condition was maintained to erase the errors. Finally, it was observed that prepared patch in capsule of amoxicillin shows better release rate than a marketed formulation of amoxicillin. As the marketed formulation shows 100% rate release in 56 minutes and the prepared one shows more than 2 hours of extent release by following a control release with zero order kinetics.

V. CONCLUSION AND FUTURE PERSPECTIVES

Drug delivery system is a formulation or device that helps to administer the drug substances inside the body to improve its efficacy, safety by controlling time, rate and route of administration. It has been a big challenge for pharmaceutical industries to have gastric residence time of conventional dosage forms. Development of Gastroretentive drug delivery system has decreased the barriers for conventional dosage forms and more researches are going for better development. Till date many studies have been done based on gastro-retentive drug delivery systems, such as development of the formulations like, Mucoadhesive, Expendable and floating systems. Most of the formulations are well known for having better gastric residence time, but have certain limitations. Mucoadhesive system is having drug drawback that it reduces the gastric motility because of its good adhesive nature. On the other hand, swellable as well as the floating systems have their limitations as they require the gastric content or special feeding of meals over which they will float as well as show their swelling property. To overcome such limitations and barriers for gastro retentive drug, Patch in Capsule is the option. Patch in Capsule is a novel formulation acting as Gastro-retentive formulation with control release effect. Patch in Capsule contains multilayer of polymeric films, which are folded and fitted in a standard size of capsule. This formulation contains polymers which show control release, unfolding mechanism, and intermediate release for combination doses. Process of formulation inside in a body will go like first it will reach to stomach where it starts to release the drug in control manner towards the upper GIT. Once the patch leaves stomach it enters into the duodenum area, where it starts to degrade. Patch having the enteric coated finishing is soluble in the Intestinal pH. By the time of administration till its elimination, it will increase the Pharmacokinetic parameters and Gastro residence time of drug without having any special meals or adhesive property. Patch in Capsule will provide different release profiles for drugs and will allow combined fixed doses.

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