FORMULATION AND EVALUATION OF PUSH-PULL OSMOTIC PUMP TABLETS OF MANGIFERIN

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ABSTRACT: Mangiferin is a xanthone compound which is abundantly present in mango leaves and has antidiabetic and other pharmacological activities. The goal is to design and evaluate a push-pull osmotic drug delivery system for mangiferin. A push-pull osmotic pump tablet is a dual-layer tablet comprising of a pull layer (drug layer) & a push layer (osmosis source layer), covered with a semipermeable membrane having water extractant and a blowing agent. The formulation was formulated using wet granulation techniques. Opadry CA was used as a film-forming polymerSodium chloride has been used as an osmotic agent. When these systems come into contact with the medium, PEO produces viscous gel and controls the release of the drug, while sodium chloride enhances drug release. in the pressure traction system. The pressure pad expands and releases the medication at a controlled rate. All pre- and post-compression settings are displayed within limits.

Keywords: Mangiferin, Push-pull osmotic pump tablets, OPADRY CA,Osmogen.

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INTRODUCTION:

Conventional dosage forms can provide adequate drug release but cannot control drug release and therapeutic content at the targeted site for a long duration. This issue was overcome by developing a controlled drug delivery system. Over the past two decades,

controlled-release formulations of more drugs have emerged. Compared to traditional dosage forms, controlled release systems have many advantages, including taking small daily or weekly doses, reducing side effects, and improving patient compliance. Timed-release products are made to keep a drug's therapeutic range consistent throughout time (1).In osmotic drug delivery systems, osmotic pressure is the key to controlled drug release. A semipermeable membrane encloses mixture of osmogen and drug. The drug will be discharged from the digestive tract at a constant rate. Osmosis is the process by which solvent molecules pass from low to high concentrations through a semipermeable membrane. Osmotic pressure, which results from the dosage form's absorption of fluid from the external environment, regulates drug delivery from the osmotic device. The rate of drug release is determined by osmotic pressure from osmotic drug delivery systems (2).

Factors influencing the Osmotic Pump tablets' drug release rate [3-5]: The following factors need to be taken into account while developing an osmotic system.

1. Nature of drug.
2. Drug solubility.
3. Osmotic Pressure.
4. Polymer type & concentration.
5. Wicking agent usage.
6. Membrane type & its characteristics.
7. Thickness of membrane.
8. Type & amount of plasticizer.
9. Delivery orifice size.

PushPull Osmotic Pump: ThePushPull Osmotic Pump is a modified EOP that allows the delivery of low and high-soluble drugs at steady rate. The system looks like an std. double-coated tablet. First does the top layer comprise the drug in the formulation of polymers, osmolytes & other tablet excipients. This polymeric osmotic agent is capable of forming a drug suspension in situ. Another layer contains penetrants and colorants, polymers & tablet excipients and is created by compressing tablets and joining them to create a single bilayer membrane. Then the core is covered by semi-permeable membrane. After covering, a laser or mechanical drill is used to punch a small hole in

the film on the tablet's drug-coated side. As the system is put in an aqueous setting, the osmotic agents of two layers draw water into the tablet. The drug layer's osmotic attraction draws water in the compartment & generates a drug suspension. The nondrug layer's osmotic agent pulls water in the compartment simultaneously, expanding its volume, and nondrug layer forces the drug solution out through the administration hole.

MATERIALS & METHOD

Materials

Table 1: Materials utilized in the present analysis

S.No	Category	Material	Source
1.	Active Pharmaceutical Ingredient	Mangiferin	Isolated in lab
2.	Polymer	Polyox N-80	Colorcon Asia Pvt. Limited Goa
3.	Polymer	Polyox WSR Coagulant	
4.	Coating Material	Opadry CA	
5.	Binder	PVP K-30	S.D Fine Chemicals, Mumbai
6.	Osomogen	Sodium Chloride	
7.	Glidant	Talc	
8.	Lubricant	Magnesium Stearate	
9.	Granulating Solvent	Isopropyl Alcohol	
10.	Coating Solvent	Acetone	

Table 2: Formulation F1-F4 formula

Ingredient	F1	F2	F3	F4
Drug	100	100	100	100
Polyox N-80	70	80	85	95
PVPK-30	20	20	20	20
Magnesium stearate	2	2	2	2
Microcrystalline cellulose	26	16	10	5
Talc	2	2	2	2
Polyox WSR	50	60	70	80

Nacl	30	30	30	30
Coloring agent	2	2	2	2
Magnesium stearate	2	2	2	2
Microcrystalline cellulose	50	40	30	20

Methods

"Push-pull osmotic pump": preparation of double-layer osmotic tablets includes the below steps:

Step1: preparation of the drug layer: granulation by wet granulation technology. All ingredients are accurately weighed and passed through a 40# sieve. Then combined with the API and the granulating agent utilized was IPA. To obtain adequate granulation, add gradually while granulating. For 20 to 25 minutes, the granules are dried at 50°C in a tray drier. Then pass via a 30# sieve to obtain homogeneous particles. Finally, the extragranular ingredients are homogeneously added to the granules.

Step 2: Push Layer Formulation: Granulation utilises wet granulation techniques. Each ingredient is accurately weighed and passed through a 40# sieve. Then mix everything evenly. IPA was used as a granulating agent. Add slowly to achieve proper granulation. For 20 to 25 minutes, the granules are dried at 50°C in a tray drier. Then pass through a 30# sieve to obtain uniform particles. Finally, the extragranular ingredients are homogeneously combined with granules.

Step 3: Bilayer tablets formulation: Formulation of the bilayer tablet using an 8-station rotary machine (Cadmac). Tablets are formed by 5 millimeters concave punches. First, the layer of drug is pre-compressed. Add pressure layer granules to cavity to cover the pre-compressed layer of drug & recompressed to form a bi-layer tablet. Adjusted hardness and weight.

Step 4: Coating of bilayer tablets: Coat the tablets using conventional coating methods. Coating parameters are as follows:

Size of Pan	6 inch
Rotation speed of Pan	30-35 rpm
Spray rate	8 to 10ml per min
Temperature	20-25ºC
Atomization air	1 to 1.5 bar

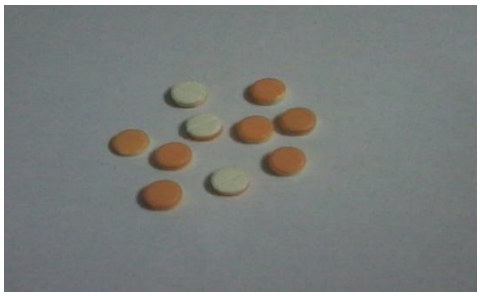

Figure 1: Prepared tablets

Compressed Tablet Rating:

1. Weight Variation: The weight and weight variation of each tablet in the batch must be within the allowable range. Randomly 20 tablets were chosen from every lot & each lot was weighed (in mg) with analytical balance. Determine the standard deviation, mean weight & relative standard deviation.

2. Thickness: Measured with a Vernier caliper. **3. Hardness:** Using the Pfizer Tablet Hardness Tester, the hardness of randomly selected 6 tablets was calculated. According to reports, Kilo Dam.

4. Friability: It has been assessed as the % loss of weight of the tablet while tumbling in the mill for four minutes at 25 turns. Then the tablets were dedusted and the loss of weight due to breakage/ abrasion was evaluated as % of friability. The friability according to IP varies from 0.5 to 1 percent of the av. weight of the tablets.

5**. Coating thickness:** The thickness of ten coated and uncoated tablets was calculated and any differences were determined. Indicate the average.

6. Content Uniformity: Take 20 tablets at random, weigh them, and pulverize them accurately.

Take a weight equivalent to 12 mg of mangiferin and dissolve it in the prescribed amount of water (500 ml). Sonicate the solution for 2 hr in a bath sonicator & set aside. Then filter the solution via a 0.45 µ nylon filter on the next day & analyzed according to the appropriate standard.

7. Dissolution studies: The release was conducted in 0.1N HCl since the mechanism is not dependent on the dissolving medium's pH. A spectrophotometer (UV-1700, Shimadzu, Japan) with a 250 nm wavelength was used to assess the content of drug.

8. Swelling studies: Swelling studies have been performed on all formulations i. e. F1 to F4. Since the rate of swelling is relevant and affects the drug release kinetics & mechanism, penetration of the dissolution medium of the matrix tablet was determined. The greatest swelling was observed in formulation F2. Tablets of each formulation (F1 to F4) were evaluated for swelling index and the results are shown.

9. Pharmacokinetic study of optimized formulation

Prior to dosing, animals were randomly assigned to two treatment groups of six animals each and were fasted for 24h with free access to water. **Group 1** animals were orally administered plain drug solution 250 mg/kg b.w, **Group 2** animals were orally received optimized formulation 250 mg/kg b.w equivalent to Mangiferin. Blood samples (0.5 ml) were carefully withdrawn from ear vein nipping at 0.5, 1, 1.5, 2, 4, 6, 8, and 12 h post administration. The withdrawn blood samples were transferred to a series of graduated centrifuge tubes containing 0.1 mL of 100 IU heparin solution. The heparinized blood samples were centrifuged at 3600 rpm and 4ºC for 10 min (Remi Centrifuge R-8C, Hyderabad, India). The supernatant plasma was transferred into another set of sample tubes and preserved below -20ºC until analyzed (Chakraborty et al., 2014; Dissanayake et al., 2012).

For drug quantification, plasma samples were defrosted to room temperature and filtered through 0.25 µm membrane filter. In order to deproteinize plasma, and subsequently extract mangiferin acetonitrile (1.0 ml) was added to plasma (0.2 ml) and the mixture was vortex-mixed for 30 s. After standing for 10 min, the mixture was centrifuged at 5000 rpm for 10 min. The upper layer (about 100 µl) was separated and filtered through nylon membrane filters (0.22 µm, 13 mm). The supernatant acetonitrile solution was evaporated to dryness and the residue was dissolved with 300 µL of the HPLC mobile phase. About 20 µl of filtrate was used for estimating mangiferin by HPLC method (Umathe et al., 2008).

The maximum plasma concentration (C max) and the time to reach the maximum concentration (T max) were directly obtained from the observed values. Other pharmacokinetic parameters including area under curve up to last sampling point (AUC last), total area under curve up to infinity (AUC total) and half life (t1/2) were obtained using PK solver 2.0 an add-in program.

10. **Stability Study:** Based on ICH guidelines, the optimized formulation was loaded into a stability chamber for three months accelerated stability study (75 ± 5% RH and 40 ± 2ºC). The optimized batches are packaged in HDPE bottles for stability studies. Samples were taken at 1, 2, and 3 months to assess drug content, physical appearance & in vitro release of drug.

RESULTS AND DISCUSSION:

Parameter	**F1**	**F2**	**F3**	**F4**

Hardness (Kp) (n=6)	6.8±0.4	6.8±0.4	6.8±0.4	6.8±0.4
Wt. variation (n=20)	Pass	Pass	Pass	Pass
Thickness (mm) (n=10)	4.21±0.3	4.13±0.3	4.33±0.3	4.20±0.2
Assay (%) (n=3)	99.7± 0.2	100.6± 0.6	99.7± 0.2	101.1± 0.2
Friability (%)	Pass	Pass	Pass	Pass
Coat thickness (µ) (n=10)	180± 40	160± 40	170± 40	190± 30 1

Table 3: Findings of various tests performed on formulations F1-F4

Pharmacokinetic parameters[a]	**Optimised formulation**	**Pure drug**
AUC_{0-t} (ng h/ml)	**3730**	**2334**
C_{max} (ng/ml)	**490.7**	**237.9**
$AUC_{0-\infty}$ (ng h/ml)	**3730**	**2334**
$T_{1/2}$ (h)	**6**	**4**
T_{max} (h)	**4**	**2**

Dissolution study:

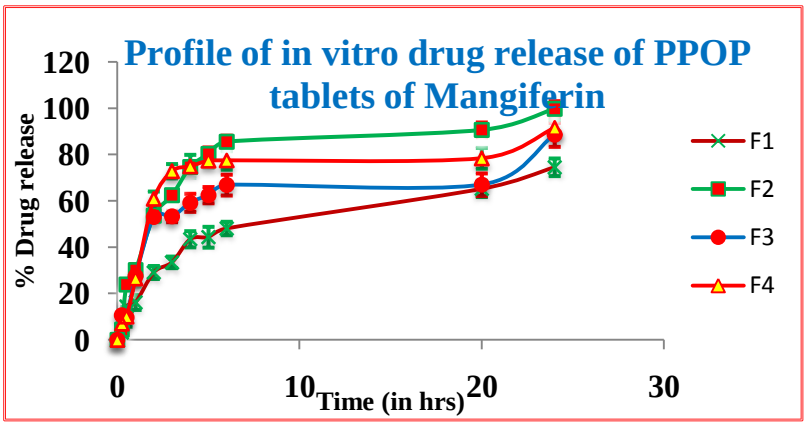

Figure 3: Dissolution profile of F1 - F4

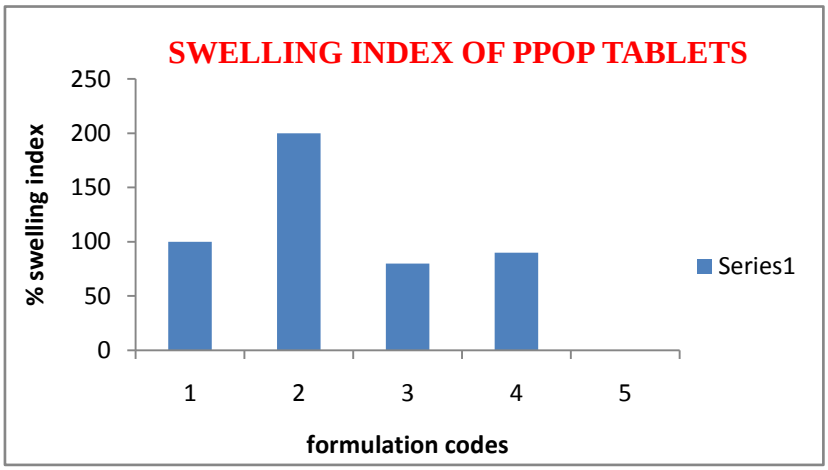

Figure 4: Swelling studies of PPOP tablets

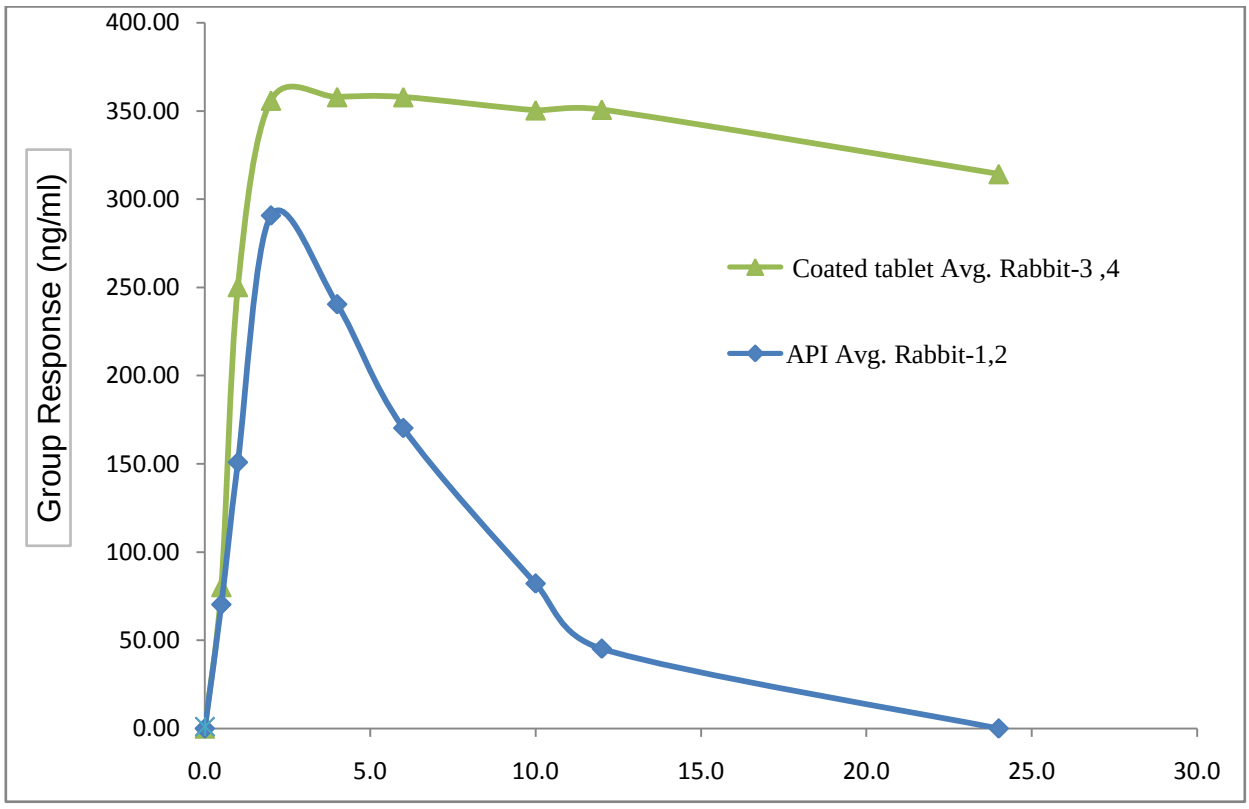

Figure 5: Pharmacokinetic graph of F2 and active pharmaceutical ingredient

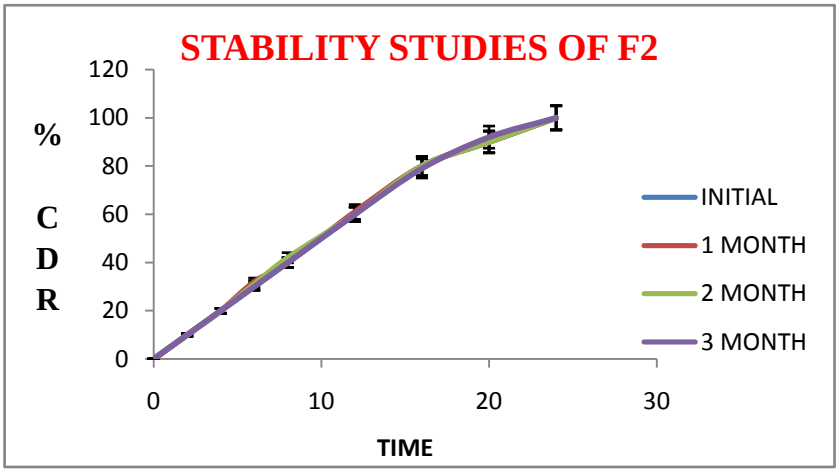

Figure 6: Stability studies of F2

CONCLUSION

In the present study, the purpose of the study has been to formulate & optimize an effective osmotic drug delivery system for mangiferin to release the drug in a controlled manner for long time. This can provide significant benefits to patients through improved efficacy and lessened side effects along with number of daily doses contrasted to traditional therapies. The optimized system has been chosen to analyze the pH impact of medium of the solution & intensity of the agitation. A push-pull osmotic pump was produced in this work and this push-pull osmotic system demonstrated the desired once-daily release kinetics. All tablet assessment parameters such as friability, hardness, drug content & release studies, etc. Very satisfied. From the optimized batch (F2), drug release has been observed to follow zero order kinetics having a regression coefficient of 0.9996. Stability studies showed that the optimized group undergoing accelerated stability studies showed no significant changes, confirming the stability of the formulation.

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